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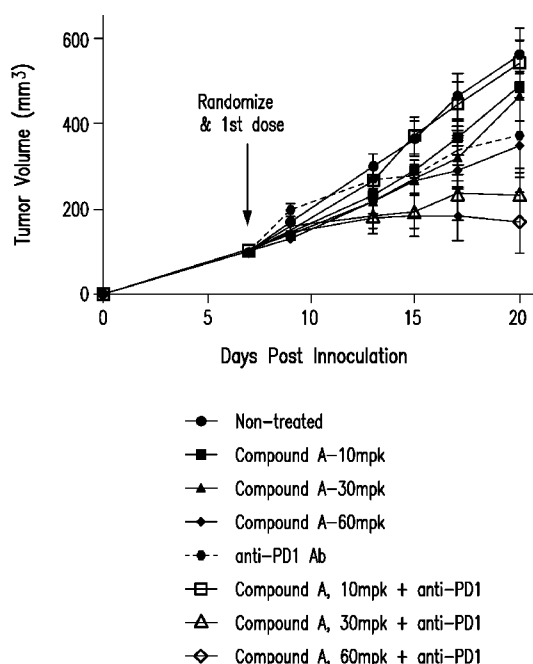
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(54) Title: COMBINATION OF IMMUNOTHERAPY AGENTS AND SPLEEN TYROSINE KINASE INHIBITORS

FIG. 1

CT26_07 Tumor Growth Curve
(mean $\pm$ sem, n = 10)



(57) Abstract: This disclosure provides new combination therapies for treating cancers. In particular, this disclosure provides methods for treating a cancer comprising administering to a subject having a cancer a therapeutically effective amount of an immunotherapy agent and a Spleen tyrosine kinase (SYK) inhibitor.

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COMBINATION OF IMMUNOTHERAPY AGENTS AND SPLEEN TYROSINE KINASE INHIBITORS

CROSS REFERENCE TO RELATED APPLICATION

[001] This application claims priority to U.S. Provisional Application Nos. 62/342,708, filed May 27, 2016 and 62/425,572, filed November 22, 2016, the disclosures of which are incorporated herein by reference in their entireties.

FIELD

[002] This disclosure provides new combination therapies for treating cancers. In particular, this disclosure provides methods for treating a cancer, comprising administering to a subject having a cancer a therapeutically effective amount of a combination comprising an immunotherapy agent and a spleen tyrosine kinase (SYK) inhibitor.

BACKGROUND

[003] Spleen tyrosine kinase (SYK) is a 72 kDa non-receptor cytoplasmic tyrosine kinase. SYK has a primary amino acid sequence similar to that of zeta-associated protein-70 (ZAP-70) and is involved in receptor-mediated signal transduction. The N-terminal domain of SYK contains two Src-homology 2 (SH2) domains, which bind to diphosphorylated immunoreceptor tyrosine-based activation motifs (ITAMs) found in the cytoplasmic signaling domains of many immunoreceptor complexes. The C-terminus contains the catalytic domain, and includes several catalytic loop autophosphorylation sites that are responsible for receptor-induced SYK activation and subsequent downstream signal propagation. SYK is expressed in many cell types involved in adaptive and innate immunity, including lymphocytes (B cells, T cells, and NK cells), granulocytes (basophils, neutrophils, and eosinophils), monocytes, macrophages, dendritic cells, and mast cells. SYK is expressed in other cell types, including airway epithelium and fibroblasts in the upper respiratory system. See, e.g., TURNER et al., *Immunology Today*, 21(3):148-54 (2000); and SANDERSON et al., *Inflammation & Allergy — Drug Targets*, 8:87-95 (2009).

[004] SYK's role in ITAM-dependent signaling and its expression in many cell types suggest that compounds which inhibit SYK activity may be useful for treating hematological malignancies, such as acute myeloid leukemia, B-cell chronic lymphocytic leukemia, B-cell lymphoma (e.g., mantle cell

lymphoma), and T-cell lymphoma (e.g., peripheral T-cell lymphoma); as well as epithelial cancers, such as lung cancer, pancreatic cancer, and colon cancer. See, e.g., HAHN et al., *Cancer Cell*, 16:281-294 (2009); CHU et al., *Immunol. Rev.*, 165:167-180 (1998); FELDMAN et al., *Leukemia*, 22:1139-43 (2008); RINALDI et al., *Br. J. Haematol.*, 132:303-316 (2006); STREUBEL et al., *Leukemia*, 20:313-18 (2006); BUCHNER et al., *Cancer Research*, 69(13):5424-32 (2009); BAUDOT et al., *Oncogene*, 28:3261-73 (2009); and SINGH et al., *Cancer Cell*, 15:489-500 (2009).

[005] It would be beneficial if more effective cancer treatment regimens could be developed. Combinations of cancer treatments that could both treat cancer, and overcome resistance to anticancer agents would be especially helpful. Thus, there is a need for new cancer treatment.

BRIEF SUMMARY

[006] In certain embodiments, the invention relates to a method of treating a cancer comprising administering to a subject having a cancer a therapeutically effective amount of a combination comprising an immunotherapy agent and a SYK inhibitor.

[007] In certain embodiments, the cancer is non-small cell lung cancer, head and neck squamous cell carcinoma, or triple negative breast cancer. In certain embodiments, the SYK inhibitor is 6-((1R,2S)-2-aminocyclohexylamino)-7-fluoro-4-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[3,4-c]pyridine-3(2H)-one citrate or a crystalline form thereof. In certain embodiments, the immunotherapy agent is nivolumab.

[008] In certain embodiments, the invention relates to a medical kit for treating a cancer comprising a therapeutically effective amount of a combination comprising an immunotherapy agent and a SYK inhibitor.

BRIEF DESCRIPTION OF THE DRAWINGS

[009] Figure 1 exemplifies an effect of Compound A, anti-PD-1, and Compound-A plus anti-PD-1 combination on tumor volumes against *in vivo* CT26 mouse syngeneic colon cancer model.

[010] Figure 2 exemplifies an effect of Compound A, anti-PD-1, and Compound-A plus anti-PD-1 combination on survival against *in vivo* CT26 mouse syngeneic colon cancer model.

[011] Figure 3 exemplifies an effect of Compound A, anti-PD-1, and Compound-A plus anti-PD-1 combination on B-cells (B220+ cells).

[012] Figure 4 exemplifies an effect of Compound A, anti-PD-1, and Compound-A plus anti-PD-1 combination on MDSCs (CD11B+ cells).

[013] Figure 5 exemplifies an effect of Compound A, anti-PD-1, and Compound-A plus anti-PD-1 combination on tumor volumes against *in vivo* 4T1 mouse syngeneic breast cancer model.

[014] Figure 6 exemplifies tumor volumes of re-challenged animals in CT-26 mouse syngeneic colon cancer model.

[015] Figure 7 exemplifies % mice with tumors for re-challenged animals in CT-26 mouse syngeneic colon cancer model.

[016] Figure 8 exemplifies an effect of Compound A, anti-PD-1, and Compound A plus anti-PD-1 combination on tumor B220+ cells in CT-26 mouse syngeneic colon cancer model.

[017] Figure 9 exemplifies an effect of Compound A, anti-PD-1, and Compound A plus anti-PD-1 combination on tumor NK+CD3-/activation (NKp46) in CT-26 mouse syngeneic colon cancer model.

[018] Figure 10 exemplifies an effect of Compound A, anti-PD-1, and Compound A plus anti-PD-1 combination on tumor F4/80+ TAMs in CT-26 mouse syngeneic colon cancer model.

[019] Figure 11 exemplifies an effect of Compound A, anti-PD-1, and Compound A plus anti-PD-1 combination on tumor CD4+ Treg in CT-26 mouse syngeneic colon cancer model.

[020] Figure 12 exemplifies an effect of Compound A on the percentage of MDSCs in the tumor infiltrating leukocytes in syngeneic B16BL6 murine melanoma model.

[021] Figure 13 exemplifies an effect of Compound A on MDSC (CD11b+) in HCC70 triple negative breast cancer xenograph model.

[022] Figure 14 exemplifies individual tumor growth of each animal in vehicle treatment group in MH-22A liver syngeneic model.

[023] Figure 15 exemplifies individual tumor growth of each animal in Compound A treatment group in MH-22A liver syngeneic model.

[024] Figure 16 exemplifies individual tumor growth of each animal in anti-PD-1 treatment group in MH-22A liver syngeneic model.

[025] Figure 17 exemplifies individual tumor growth of each animal in Compound A + anti-PD-1 treatment group in MH-22A liver syngeneic model.

[026] Figure 18 exemplifies average tumor volume over time in female C3H/HeN mice bearing MH-22A syngeneic model dosed with vehicle, Compound A, anti-PD-1, or Compound-A plus anti-PD-1 combination.

[027] Figure 19 exemplifies average tumor volume over time for the untreated female C3H mice or the tumor-free survivors from previous study (which were treated with Compound A and anti-PD-1 combination in the previous study) after re-challenge with MH-22A syngeneic model.

[028] Figure 20 exemplifies an individual tumor volume over time of tumor-free survivors from previous study (where mice were treated with Compound A and anti-PD-1 combination) after re-challenge with MH-22A syngeneic model.

DETAILED DESCRIPTION

[029] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this disclosure belongs. All patents and publications referred to herein are incorporated by reference in their entirety.

DEFINITIONS

[030] The term “Spleen tyrosine kinase” used herein refers to any member of the Syk family of tyrosine kinases. SYK is a 72 kDa non-receptor cytoplasmic tyrosine kinase.

[031] The term “Spleen tyrosine kinase inhibitor” or “SYK inhibitor” used herein refers to a compound having the ability to interact with Spleen tyrosine kinase and inhibit its enzymatic activity.

[032] As used herein, the terms “treatment,” “treat,” and “treating” are meant to include the full spectrum of intervention for the cancer from which the subject is suffering, such as administration of the combination to alleviate, slow, stop, or reverse one or more symptoms of the cancer or to delay the progression of the cancer even if the cancer is not actually eliminated. Treatment can include, for example, a decrease in the severity of a symptom, the number of symptoms, or frequency of relapse, e.g., the inhibition of tumor growth, the arrest of tumor growth, or the regression of already existing tumors.

[033] The term “subject”, as used herein, means a mammal, and “mammal” includes, but is not limited to, a human. In certain embodiments, the subject has been treated with an agent, e.g., an immunotherapy agent and/or an SYK inhibitor, prior to initiation of treatment according to the

method of the disclosure. In certain embodiments, the subject is at risk of developing or experiencing a recurrence of a cancer. In certain embodiments, the subject is a cancer patient.

[034] The term “anti-cancer agent”, “anti-tumor agent” or “chemotherapeutic agent” refers to any agent useful in the treatment of a neoplastic condition. One class of anti-cancer agents comprises chemotherapeutic agents.

[035] The term “effective amount” or “therapeutically effective amount” refers to that the amount of a compound, or combination of one or more compounds when administered (either sequentially or simultaneously) that elicits the desired biological or medicinal response, e.g., either destroys the target cancer cells or slows or arrests the progression of the cancer in a subject. The therapeutically effective amount may vary depending upon the intended application (in vitro or in vivo), or the subject and disease condition being treated, e.g., the weight and age of the subject, the severity of the disease condition, the manner of administration and the like, which can readily be determined by one skilled in the art. The term also applies to a dose that will induce a particular response in target cells, e.g., reduction of platelet adhesion and/or cell migration. For example, the “therapeutically effective amount” as used herein refers to the amount of an immunotherapy agent and the amount of a SYK inhibitor that, when administered in combination have a beneficial effect. In certain embodiments, the combined effect is additive. In certain embodiments, the combined effect is synergistic. Further, it will be recognized by one skilled in the art that in the case of combination therapy, the amount of the immunotherapy agent and/or the amount of the SYK inhibitor may be used in a “sub-therapeutic amount”, i.e., less than the therapeutically effective amount of the immunotherapy agent or SYK inhibitor alone.

[036] The term “about” refers to approximately, in the region of, roughly, or around. When the term “about” is used in conjunction with a number or a numerical range, it means that the number or numerical range referred to is an approximation within experimental variability (or within statistical experimental error), and thus the number or numerical range may vary from, for example, between 1% and 15% of the stated number or numerical range. In general, the term “about” is used herein to modify a numerical value above and below the stated value by a variance of $\pm 10\%$.

[037] The term “combination administration,” or “administered in combination” refers to administering of more than one pharmaceutically active ingredients (including but not limited to an immunotherapy agent and an SYK inhibitor as disclosed herein) to a subject. Combination administration may refer to simultaneous administration or may refer to sequential administration of the immunotherapy agent and the SYK inhibitor as disclosed herein.

[038] The terms “simultaneous” and “simultaneously” refer to the administration of the immunotherapy agent and the SYK inhibitor as disclosed herein, to a subject at the same time, or at two different time points that are separated by no more than 2 hours.

[039] The terms “sequential” and “sequentially” refer to the administration of the immunotherapy agent and the SYK inhibitor as disclosed herein, to a subject at two different time points that are separated by more than 2 hours, e.g., about 3 hours, 4 hours, 5 hours, about 8 hours, 12 hours, 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days or even longer.

[040] The term “synergistic effect” refers to a situation where the combination of two or more agents produces a greater effect than the sum of the effects of each of the individual agents. The term encompasses not only a reduction in symptoms of the disorder to be treated, but also an improved side effect profile, improved tolerability, improved patient compliance, improved efficacy, or any other improved clinical outcome.

[041] The term a “sub-therapeutic amount” of an agent or therapy is an amount less than the effective amount for that agent or therapy as a single agent, but when combined with an effective or sub-therapeutic amount of another agent or therapy can produce a result desired by the physician, due to, for example, synergy in the resulting efficacious effects, or reduced side effects.

[042] The term “pharmaceutically acceptable salt” refers to salts derived from a variety of organic and inorganic counter ions well known in the art. Pharmaceutically acceptable acid addition salts may be formed with inorganic acids and organic acids. For reviews of suitable salts, see, e.g., BERGE et al, J. Pharm. Sci. 66:1-19 (1977) and Remington: The Science and Practice of Pharmacy, 20th Ed., ed. A. Gennaro, Lippincott Williams & Wilkins, 2000. Non-limiting examples of suitable acid salts includes: hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, lactate acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like. Non-limiting examples of suitable base salts includes: sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like, specifically such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine.

[043] The term “pharmaceutically acceptable carrier” or “pharmaceutically acceptable excipient” includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions of the disclosure is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

[044] The terms “carrier”, “adjuvant”, or “vehicle” are used interchangeably herein, and include any and all solvents, diluents, and other liquid vehicles, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. Remington: The Science and Practice of Pharmacy, 20th Ed., ed. A. Gennaro, Lippincott Williams & Wilkins, 2000 discloses various carriers used in formulating pharmaceutically acceptable compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier medium is incompatible with the compounds of the disclosure, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutically acceptable composition, its use is contemplated to be within the scope of this disclosure.

[045] Unless otherwise stated, compounds described herein include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structure except for the replacement of a hydrogen atom by a deuterium or tritium, or the replacement of a carbon atom by a ^{13}C - or ^{14}C -enriched carbon are within the scope of the disclosure.

[046] Unless otherwise stated, compounds described herein include all stereochemical forms of the structure; i.e., the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the disclosure. In the compounds described herein where relative stereochemistry is defined, the diastereomeric purity of such a compound may be at least 80%, at least 90%, at least 95%, or at least 99%. As used herein, the term “diastereomeric purity” refers to the amount of a compound having the depicted relative stereochemistry, expressed as a percentage of the total amount of all diastereomers present.

[047] “Substituted,” when used in connection with a chemical substituent or moiety (e.g., an alkyl group), means that one or more hydrogen atoms of the substituent or moiety have been replaced with

one or more non-hydrogen atoms or groups, provided that valence requirements are met and that a chemically stable compound results from the substitution.

[048] The term “alkyl” refers to straight chain and branched saturated hydrocarbon groups, generally having a specified number of carbon atoms (e.g., C₁₋₃ alkyl refers to an alkyl group having 1 to 3 carbon atoms, C₁₋₆ alkyl refers to an alkyl group having 1 to 6 carbon atoms, and so on). Examples of alkyl groups include methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *s*-butyl, *i*-butyl, *t*-butyl, pent-1-yl, pent-2-yl, pent-3-yl, 3-methylbut-1-yl, 3-methylbut-2-yl, 2-methylbut-2-yl, 2,2,2-trimethyleth-1-yl, *n*-hexyl, and the like.

[049] “Alkenyl” refers to straight chain and branched hydrocarbon groups having one or more carbon-carbon double bonds, and generally having a specified number of carbon atoms. Examples of alkenyl groups include ethenyl, 1-propen-1-yl, 1-propen-2-yl, 2-propen-1-yl, 1-buten-1-yl, 1-buten-2-yl, 3-buten-1-yl, 3-buten-2-yl, 2-buten-1-yl, 2-buten-2-yl, 2-methyl-1-propen-1-yl, 2-methyl-2-propen-1-yl, 1,3-butadien-1-yl, 1,3-butadien-2-yl, and the like.

[050] “Alkynyl” refers to straight chain or branched hydrocarbon groups having one or more triple carbon-carbon bonds, and generally having a specified number of carbon atoms. Examples of alkynyl groups include ethynyl, 1-propyn-1-yl, 2-propyn-1-yl, 1-butyn-1-yl, 3-butyn-1-yl, 3-butyn-2-yl, 2-butyn-1-yl, and the like.

[051] “Halo,” “halogen” and “halogeno” may be used interchangeably and refer to fluoro, chloro, bromo, and iodo.

[052] “Haloalkyl,” “haloalkenyl,” and “haloalkynyl,” refer, respectively, to alkyl, alkenyl, and alkynyl groups substituted with one or more halogen atoms, where alkyl, alkenyl, and alkynyl are defined above, and generally having a specified number of carbon atoms. Examples of haloalkyl groups include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, and the like.

[053] “Cycloalkyl” refers to saturated monocyclic and bicyclic hydrocarbon groups, generally having a specified number of carbon atoms that comprise the ring or rings (e.g., C₃₋₈ cycloalkyl refers to a cycloalkyl group having 3 to 8 carbon atoms as ring members). Bicyclic hydrocarbon groups may include isolated rings (two rings sharing no carbon atoms), spiro rings (two rings sharing one carbon atom), fused rings (two rings sharing two carbon atoms and the bond between the two common carbon atoms), and bridged rings (two rings sharing two carbon atoms, but not a common bond). The cycloalkyl group may be attached to a parent group or to a substrate at any ring atom

unless such attachment would violate valence requirements. In addition, the cycloalkyl group may include one or more non-hydrogen substituents unless such substitution would violate valence requirements.

[054] Examples of monocyclic cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like. Examples of fused bicyclic cycloalkyl groups include bicyclo[2.1.0]pentanyl (i.e., bicyclo[2.1.0]pentan-1-yl, bicyclo[2.1.0]pentan-2-yl, and bicyclo[2.1.0]pentan-5-yl), bicyclo[3.1.0]hexanyl, bicyclo[3.2.0]heptanyl, bicyclo[4.1.0]heptanyl, bicyclo[3.3.0]octanyl, bicyclo[4.2.0]octanyl, bicyclo[4.3.0]nonanyl, bicyclo[4.4.0]decanyl, and the like. Examples of bridged cycloalkyl groups include bicyclo[2.1.1]hexanyl, bicyclo[2.2.1]heptanyl, bicyclo[3.1.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo[3.2.1]octanyl, bicyclo[4.1.1]octanyl, bicyclo[3.3.1]nonanyl, bicyclo[4.2.1]nonanyl, bicyclo[3.3.2]decanyl, bicyclo[4.2.2]decanyl, bicyclo[4.3.1]decanyl, bicyclo[3.3.3]undecanyl, bicyclo[4.3.2]undecanyl, bicyclo[4.3.3]dodecanyl, and the like. Examples of spiro cycloalkyl groups include spiro[3.3]heptanyl, spiro[2.4]heptanyl, spiro[3.4]octanyl, spiro[2.5]octanyl, spiro[3.5]nonanyl, and the like. Examples of isolated bicyclic cycloalkyl groups include those derived from bi(cyclobutane), cyclobutanecyclopentane, bi(cyclopentane), cyclobutanecyclohexane, cyclopentanecyclohexane, bi(cyclohexane), etc.

[055] As used herein, “aryl” refers to fully unsaturated monocyclic aromatic hydrocarbons and to polycyclic hydrocarbons having at least one aromatic ring, both monocyclic and polycyclic aryl groups generally having a specified number of carbon atoms that comprise their ring members (e.g., C₆₋₁₄ aryl refers to an aryl group having 6 to 14 carbon atoms as ring members). The aryl group may be attached to a parent group or to a substrate at any ring atom and may include one or more non-hydrogen substituents unless such attachment or substitution would violate valence requirements. Examples of aryl groups include phenyl, biphenyl, cyclobutabenzenyl, indenyl, naphthalenyl, benzocycloheptanyl, biphenylenyl, fluorenyl, groups derived from cycloheptatriene cation, and the like.

[056] “Heterocycle” and “heterocyclyl” may be used interchangeably and refer to saturated or partially unsaturated monocyclic or bicyclic groups having ring atoms composed of carbon atoms and 1 to 4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. Both the monocyclic and bicyclic groups generally have a specified number of carbon atoms in their ring or rings (e.g., C₂₋₅ heterocyclyl refers to a heterocyclyl group having 2 to 5 carbon atoms and 1 to 4 heteroatoms as ring members). As with bicyclic cycloalkyl groups, bicyclic heterocyclyl groups may include isolated rings, spiro rings, fused rings, and bridged rings. The heterocyclyl group may

be attached to a parent group or to a substrate at any ring atom and may include one or more non-hydrogen substituents unless such attachment or substitution would violate valence requirements or result in a chemically unstable compound. Examples of monocyclic heterocyclyl groups include oxiranyl, thiaranyl, aziridinyl (e.g., aziridin-1-yl and aziridin-2-yl), oxetanyl, thiatanyl, azetidiny, tetrahydrofuranyl, tetrahydrothiopheneyl, pyrrolidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperidinyl, 1,4-dioxanyl, 1,4-oxathianyl, morpholinyl, 1,4-dithianyl, piperazinyl, 1,4-azathianyl, oxepanyl, thiepanyl, azepanyl, 1,4-dioxepanyl, 1,4-oxathiepanyl, 1,4-oxaazepanyl, 1,4-dithiepanyl, 1,4-thiazepanyl, 1,4-diazepanyl, 3,4-dihydro-2*H*-pyranyl, 5,6-dihydro-2*H*-pyranyl, 2*H*-pyranyl, 1,2,3,4-tetrahydropyridinyl, and 1,2,5,6-tetrahydropyridinyl.

[057] “Heteroaryl” refers to unsaturated monocyclic aromatic groups and to polycyclic groups having at least one aromatic ring, each of the groups having ring atoms composed of carbon atoms and 1 to 4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. Both the monocyclic and polycyclic groups generally have a specified number of carbon atoms as ring members (e.g., C₁₋₉ heteroaryl refers to a heteroaryl group having 1 to 9 carbon atoms and 1 to 4 heteroatoms as ring members) and may include any bicyclic group in which any of the above-listed monocyclic heterocycles are fused to a benzene ring. The heteroaryl group may be attached to a parent group or to a substrate at any ring atom and may include one or more non-hydrogen substituents unless such attachment or substitution would violate valence requirements or result in a chemically unstable compound. Examples of heteroaryl groups include monocyclic groups such as pyrrolyl (e.g., pyrrol-1-yl, pyrrol-2-yl, and pyrrol-3-yl), furanyl, thiopheneyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isothiazolyl, thiazolyl, 1,2,3-triazolyl, 1,3,4-triazolyl, 1-oxa-2,3-diazolyl, 1-oxa-2,4-diazolyl, 1-oxa-2,5-diazolyl, 1-oxa-3,4-diazolyl, 1-thia-2,3-diazolyl, 1-thia-2,4-diazolyl, 1-thia-2,5-diazolyl, 1-thia-3,4-diazolyl, tetrazolyl, pyridinyl, pyridazinyl, pyrimidinyl, and pyrazinyl.

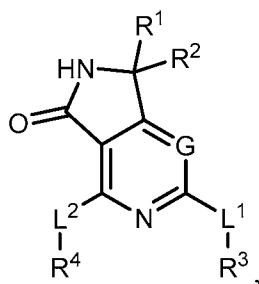
[058] Examples of heteroaryl groups also include bicyclic groups such as benzofuranyl, isobenzofuranyl, benzothiopheneyl, benzo[*c*]thiopheneyl, indolyl, 3*H*-indolyl, isoindolyl, 1*H*-isoindolyl, indolinyl, isoindolinyl, benzimidazolyl, indazolyl, benzotriazolyl, 1*H*-pyrrolo[2,3-*b*]pyridinyl, 1*H*-pyrrolo[2,3-*c*]pyridinyl, 1*H*-pyrrolo[3,2-*c*]pyridinyl, 1*H*-pyrrolo[3,2-*b*]pyridinyl, 3*H*-imidazo[4,5-*b*]pyridinyl, 3*H*-imidazo[4,5-*c*]pyridinyl, 1*H*-pyrazolo[4,3-*b*]pyridinyl, 1*H*-pyrazolo[4,3-*c*]pyridinyl, 1*H*-pyrazolo[3,4-*c*]pyridinyl, 1*H*-pyrazolo[3,4-*b*]pyridinyl, 7*H*-purinyl, indolizinyl, imidazo[1,2-*a*]pyridinyl, imidazo[1,5-*a*]pyridinyl, pyrazolo[1,5-*a*]pyridinyl, pyrrolo[1,2-*b*]pyridazinyl, imidazo[1,2-*c*]pyrimidinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, 1,6-naphthyridinyl, 1,7-naphthyridinyl, 1,8-naphthyridinyl, 1,5-

naphthyridinyl, 2,6-naphthyridinyl, 2,7-naphthyridinyl, pyrido[3,2-*d*]pyrimidinyl, pyrido[4,3-*d*]pyrimidinyl, pyrido[3,4-*d*]pyrimidinyl, pyrido[2,3-*d*]pyrimidinyl, pyrido[2,3-*b*]pyrazinyl, pyrido[3,4-*b*]pyrazinyl, pyrimido[5,4-*d*]pyrimidinyl, pyrazino[2,3-*b*]pyrazinyl, and pyrimido[4,5-*d*]pyrimidinyl.

[059] “Oxo” refers to a double bonded oxygen (=O).

SYK inhibitors

[060] In certain embodiments, the SYK inhibitor is a compound of Formula I,



or a pharmaceutically acceptable salt thereof, wherein:

G is C(R⁵);

L¹ and L² are each independently selected from -NH- and a bond;

R¹ and R² are each independently selected from hydrogen, halo, C₁₋₃ alkyl, and C₁₋₃ haloalkyl, or R¹ and R², together with the atom to which they are attached, form a C₃₋₆ cycloalkyl;

R³ is selected from C₂₋₆ alkyl, C₃₋₈ cycloalkyl, C₂₋₅ heterocyclyl, and C₁₋₉ heteroaryl, each optionally substituted with from one to five substituents independently selected from halo, oxo, -NO₂, -CN, R⁶, and R⁷;

R⁴ is selected from C₃₋₈ cycloalkyl, C₂₋₅ heterocyclyl, C₆₋₁₄ aryl, and C₁₋₉ heteroaryl, each optionally substituted with from one to five substituents independently selected from halo, oxo, -CN, R⁶, and R⁷;

R⁵ is selected from hydrogen, halo, -CN, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₂₋₅ heterocyclyl, C₁₋₅ heteroaryl, and R¹⁰, wherein the alkyl, alkenyl, alkynyl moieties are each optionally substituted with from one to five substituents independently selected from halo, -CN, oxo, and R¹⁰, and wherein the heterocyclyl moiety has 3 to 6 ring atoms and the heteroaryl moiety has 5 or 6 ring atoms, and the heterocyclyl and heteroaryl moieties are each optionally substituted with from one to four

substituents independently selected from halo, $-\text{NO}_2$, $-\text{CN}$, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, and R^{10} ;

each R^6 is independently selected from $-\text{OR}^8$, $-\text{N}(\text{R}^8)\text{R}^9$, $-\text{NR}^8\text{C}(\text{O})\text{R}^9$, $-\text{C}(\text{O})\text{R}^8$, $-\text{C}(\text{O})\text{OR}^8$, $-\text{C}(\text{O})\text{N}(\text{R}^8)\text{R}^9$, $-\text{C}(\text{O})\text{N}(\text{R}^8)\text{OR}^9$, $-\text{C}(\text{O})\text{N}(\text{R}^8)\text{S}(\text{O})_2\text{R}^9$, $-\text{N}(\text{R}^8)\text{S}(\text{O})_2\text{R}^9$, $-\text{S}(\text{O})_n\text{R}^8$, and $-\text{S}(\text{O})_2\text{N}(\text{R}^8)\text{R}^9$;

each R^7 is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl- $(\text{CH}_2)_m$, C_{6-14} aryl- $(\text{CH}_2)_m$, C_{2-5} heterocyclyl- $(\text{CH}_2)_m$, and C_{1-9} heteroaryl- $(\text{CH}_2)_m$, each optionally substituted with from one to five substituents independently selected from halo, oxo, $-\text{NO}_2$, $-\text{CN}$, C_{1-6} alkyl, C_{1-6} haloalkyl, and R^{10} ;

each R^8 and R^9 is independently selected from hydrogen or from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl- $(\text{CH}_2)_m$, C_{6-14} aryl- $(\text{CH}_2)_m$, C_{2-5} heterocyclyl- $(\text{CH}_2)_m$, and C_{1-9} heteroaryl- $(\text{CH}_2)_m$, each optionally substituted with from one to five substituents independently selected from halo, oxo, $-\text{NO}_2$, $-\text{CN}$, C_{1-6} alkyl, C_{1-6} haloalkyl, and R^{10} ;

each R^{10} is independently selected from $-\text{OR}^{11}$, $-\text{N}(\text{R}^{11})\text{R}^{12}$, $-\text{N}(\text{R}^{11})\text{C}(\text{O})\text{R}^{12}$, $-\text{C}(\text{O})\text{R}^{11}$, $-\text{C}(\text{O})\text{OR}^{11}$, $-\text{C}(\text{O})\text{N}(\text{R}^{11})\text{R}^{12}$, $-\text{C}(\text{O})\text{N}(\text{R}^{11})\text{OR}^{12}$, $-\text{C}(\text{O})\text{N}(\text{R}^{11})\text{S}(\text{O})_2\text{R}^{12}$, $-\text{NR}^{11}\text{S}(\text{O})_2\text{R}^{12}$, $-\text{S}(\text{O})_n\text{R}^{11}$, and $-\text{S}(\text{O})_2\text{N}(\text{R}^{11})\text{R}^{12}$;

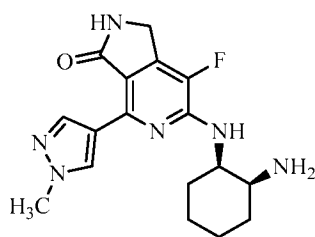
each R^{11} and R^{12} is independently selected from hydrogen and C_{1-6} alkyl;

each n is independently selected from 0, 1 and 2; and

each m is independently selected from 0, 1, 2, 3, and 4;

wherein each of the aforementioned heteroaryl moieties has one to four heteroatoms independently selected from N, O, and S, and each of the aforementioned heterocyclyl moieties is saturated or partially unsaturated and has one or two heteroatoms independently selected from N, O, and S.

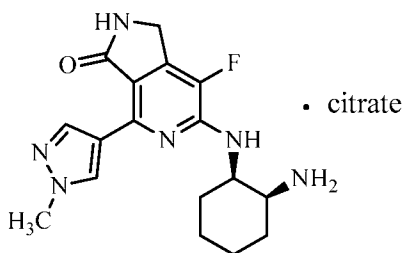
[061] In certain embodiments, the SYK inhibitor is a compound of Formula II, or 6-((1R,2S)-2-aminocyclohexylamino)-7-fluoro-4-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[3,4-c]pyridine-3(2H)-one:



(II)

or a pharmaceutically acceptable salt thereof.

[062] In certain embodiments, the SYK inhibitor is a compound of Formula III, or 6-((1R,2S)-2-aminocyclohexylamino)-7-fluoro-4-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[3,4-c]pyridine-3(2H)-one citrate:



(III)

or a crystalline form thereof. This compound may also be referred to as Compound A.

[063] The compounds of Formula I, Formula II and Formula III are described in WO 2011/079051, US 8,440,689, and US 14/973180. They may be prepared by methods known to one skilled in the art and/or according to the methods described in WO 2011/022439, US 8,440,689, and US 14/973180, each of which is hereby incorporated by reference in its entirety.

Methods of treatments and/or medical uses

[064] In certain embodiments, the invention relates to a method of treating a neoplastic condition, such as a cancer, comprising administering to a subject having a neoplastic condition a therapeutically effective amount of a combination comprising an immunotherapy agent and a SYK inhibitor.

[065] In certain embodiments, the neoplastic condition (e.g., cancer) is a solid tumor. In certain embodiments, the cancer is selected from breast cancer, lung cancer, head and neck cancer, melanoma, renal cancer, liver cancer, pancreatic cancer, colorectal cancer, ovarian cancer, gastric cancer, endometrial cancer, prostate cancer, brain and spine cancer, fallopian tube cancer, uterine cancer, bladder cancer, esophageal cancer, biliary tract cancer, urothelial cancer, soft tissue cancer, rectal cancer, thyroid cancer, bone cancer, salivary gland cancer, nasal cavity and paranasal sinus cancer, testicular cancer, adrenocortical cancer, thymic cancer, eye cancer, and gallbladder cancer.

[066] In certain embodiments, the cancer is selected from breast cancer, lung cancer, and head and neck cancer. In certain embodiments, the cancer is triple negative breast cancer (TNBC). In certain embodiments, the cancer is non-small cell lung cancer (NSCLC). In certain embodiments, the cancer is head and neck squamous cell carcinoma (HNSCC).

[067] In certain embodiments, the immunotherapy agent is an anti-PD-1 or anti-PD-L1 agent, such as an anti-PD-1 or anti-PD-L1 antibody. In certain embodiments, the immunotherapy agent is selected from pembrolizumab and nivolumab. In certain embodiments, the immunotherapy agent is pembrolizumab. In certain embodiments, the immunotherapy agent is nivolumab.

[068] In certain embodiments, the SYK inhibitor is a compound of Formula I, II, or III. In certain embodiments, the SYK inhibitor is a compound of Formula II or a pharmaceutically acceptable salt thereof. In certain embodiments, the SYK inhibitor is a compound of Formula III or a crystalline form thereof.

[069] In certain embodiments the invention relates to a method for treating a cancer selected from breast cancer, lung cancer, head and neck cancer, melanoma, renal cancer, liver cancer, pancreatic cancer, colorectal cancer, ovarian cancer, gastric cancer, endometrial cancer, prostate cancer, brain and spine cancer, fallopian tube cancer, uterine cancer, bladder cancer, esophageal cancer, biliary tract cancer, urothelial cancer, soft tissue cancer, rectal cancer, thyroid cancer, bone cancer, salivary gland cancer, nasal cavity and paranasal sinus cancer, testicular cancer, adrenocortical cancer, thymic cancer, eye cancer, and gallbladder cancer comprising administering to a subject having a cancer selected from breast cancer, lung cancer, head and neck cancer, melanoma, renal cancer, liver cancer, pancreatic cancer, colorectal cancer, ovarian cancer, gastric cancer, endometrial cancer, prostate cancer, brain and spine cancer, fallopian tube cancer, uterine cancer, bladder cancer, esophageal cancer, biliary tract cancer, urothelial cancer, soft tissue cancer, rectal cancer, thyroid cancer, bone cancer, salivary gland cancer, nasal cavity and paranasal sinus cancer, testicular cancer, adrenocortical cancer, thymic cancer, eye cancer, and gallbladder cancer a therapeutically effective amount of a combination comprising an immunotherapy agent and a SYK inhibitor. In certain embodiments the invention relates to a method for treating a cancer selected from breast cancer, lung cancer, and head and neck cancer, comprising administering to a subject having a cancer selected from breast cancer, lung cancer, and head and neck cancer a therapeutically effective amount of a combination comprising an immunotherapy agent and a SYK inhibitor. In certain embodiments the invention relates to a method for treating a cancer selected from TNBC, NSCLC, or HNSCC, comprising administering to a subject having a cancer selected from TNBC, NSCLC, or HNSCC a therapeutically effective amount of a combination comprising an immunotherapy agent and a SYK inhibitor. In certain embodiments, the immunotherapy agent is an anti-PD-1 or anti-PD-L1 agent, such as an anti-PD-1 or anti-PD-L1 antibody. In certain embodiments, the immunotherapy agent is selected from pembrolizumab and nivolumab. In certain embodiments, the immunotherapy agent is

pembrolizumab. In certain embodiments, the immunotherapy agent is nivolumab. In certain embodiments, the SYK inhibitor is a compound of Formula I, Formula II, or Formula III. In certain embodiments, the SYK inhibitor is a compound of Formula II or a pharmaceutically acceptable salt thereof. In certain embodiments, the SYK inhibitor is a compound of Formula III or a crystalline form thereof.

[070] In certain embodiments, the cancer is breast cancer. In certain embodiments, the breast cancer is hormone receptor negative. In certain embodiments, the breast cancer is HER2 negative. In certain embodiments, the breast cancer is triple negative breast cancer. In certain embodiments, the invention relates to a method for treating breast cancer (e.g., triple negative breast cancer) comprising administering to a subject having breast cancer a therapeutically effective amount of a combination comprising an immunotherapy agent and a SYK inhibitor. In certain embodiments, the immunotherapy agent is an anti-PD-1 or anti-PD-L1 agent, such as an anti-PD-1 or anti-PD-L1 antibody. In certain embodiments, the immunotherapy agent is selected from pembrolizumab and nivolumab. In certain embodiments, the immunotherapy agent is pembrolizumab. In certain embodiments, the immunotherapy agent is nivolumab. In certain embodiments, the SYK inhibitor is a compound of Formula I, Formula II, or Formula III. In certain embodiments, the SYK inhibitor is a compound of Formula II or a pharmaceutically acceptable salt thereof. In certain embodiments, the SYK inhibitor is a compound of Formula III or a crystalline form thereof.

[071] In certain embodiments, the cancer is lung cancer. In certain embodiments, the cancer is non-small cell lung cancer. In certain embodiments, the non-small cell lung cancer is squamous non-small cell lung cancer. In certain embodiments, the non-small cell lung cancer is non-squamous non-small cell lung cancer. In certain embodiments, the cancer is small cell lung cancer. In certain embodiments, the invention relates to a method for treating lung cancer (e.g., non-small cell lung cancer or small cell lung cancer) comprising administering to a subject having lung cancer a therapeutically effective amount of a combination comprising an immunotherapy agent and a SYK inhibitor. In certain embodiments, the immunotherapy agent is an anti-PD-1 or anti-PD-L1 agent, such as an anti-PD-1 or anti-PD-L1 antibody. In certain embodiments, the immunotherapy agent is selected from pembrolizumab and nivolumab. In certain embodiments, the immunotherapy agent is pembrolizumab. In certain embodiments, the immunotherapy agent is nivolumab. In certain embodiments, the SYK inhibitor is a compound of Formula I, Formula II, or Formula III. In certain embodiments, the SYK inhibitor is a compound of Formula II or a pharmaceutically acceptable salt

thereof. In certain embodiments, the SYK inhibitor is a compound of Formula III or a crystalline form thereof.

[072] In certain embodiments, the cancer is head and neck cancer. In certain embodiments, the head and neck cancer is head and neck squamous cell carcinoma (HNSCC). In certain embodiments, the invention relates to a method for treating head and neck cancer (e.g., HNSCC) comprising administering to a subject having head and neck cancer a therapeutically effective amount of a combination comprising an immunotherapy agent and a SYK inhibitor. In certain embodiments, the immunotherapy agent is an anti-PD-1 or anti-PD-L1 agent, such as an anti-PD-1 or anti-PD-L1 antibody. In certain embodiments, the immunotherapy agent is selected from pembrolizumab and nivolumab. In certain embodiments, the immunotherapy agent is pembrolizumab. In certain embodiments, the immunotherapy agent is nivolumab. In certain embodiments, the SYK inhibitor is a compound of Formula I, Formula II, or Formula III. In certain embodiments, the SYK inhibitor is a compound of Formula II or a pharmaceutically acceptable salt thereof. In certain embodiments, the SYK inhibitor is a compound of Formula III or a crystalline form thereof.

[073] In certain embodiments, the cancer is melanoma. In certain embodiments, the invention relates to a method for treating melanoma comprising administering to a subject having melanoma a therapeutically effective amount of a combination comprising an immunotherapy agent and a SYK inhibitor. In certain embodiments, the immunotherapy agent is an anti-PD-1 or anti-PD-L1 agent, such as an anti-PD-1 or anti-PD-L1 antibody. In certain embodiments, the immunotherapy agent is selected from pembrolizumab and nivolumab. In certain embodiments, the immunotherapy agent is pembrolizumab. In certain embodiments, the immunotherapy agent is nivolumab. In certain embodiments, the SYK inhibitor is a compound of Formula I, Formula II, or Formula III. In certain embodiments, the SYK inhibitor is a compound of Formula II or a pharmaceutically acceptable salt thereof. In certain embodiments, the SYK inhibitor is a compound of Formula III a crystalline form thereof.

[074] In certain embodiments, the cancer is renal cancer. In certain embodiments, the renal cancer is renal cell carcinoma (RCC). In certain embodiments, the invention relates to a method for renal cancer (e.g., RCC) comprising administering to a subject having renal cancer a therapeutically effective amount of a combination comprising an immunotherapy agent and a SYK inhibitor. In certain embodiments, the immunotherapy agent is an anti-PD-1 or anti-PD-L1 agent, such as an anti-PD-1 or anti-PD-L1 antibody. In certain embodiments, the immunotherapy agent is selected from

pembrolizumab and nivolumab. In certain embodiments, the immunotherapy agent is pembrolizumab. In certain embodiments, the immunotherapy agent is nivolumab. In certain embodiments, the SYK inhibitor is a compound of Formula I, Formula II, or Formula III. In certain embodiments, the SYK inhibitor is a compound of Formula II or a pharmaceutically acceptable salt thereof. In certain embodiments, the SYK inhibitor is a compound of Formula III or a crystalline form thereof.

[075] In certain embodiments, the cancer is liver cancer. In certain embodiments, the liver cancer is hepatocellular carcinoma (HCC). In certain embodiments, the invention relates to a method for treating liver cancer (e.g., HCC) comprising administering to a subject having liver cancer a therapeutically effective amount of a combination comprising an immunotherapy agent and a SYK inhibitor. In certain embodiments, the immunotherapy agent is an anti-PD-1 or anti-PD-L1 agent, such as an anti-PD-1 or anti-PD-L1 antibody. In certain embodiments, the immunotherapy agent is selected from pembrolizumab and nivolumab. In certain embodiments, the immunotherapy agent is pembrolizumab. In certain embodiments, the immunotherapy agent is nivolumab. In certain embodiments, the SYK inhibitor is a compound of Formula I, Formula II, or Formula III. In certain embodiments, the SYK inhibitor is a compound of Formula II or a pharmaceutically acceptable salt thereof. In certain embodiments, the SYK inhibitor is a compound of Formula III or a crystalline form thereof.

[076] In certain embodiments, the cancer is pancreatic cancer. In certain embodiments, the invention relates to a method for treating pancreatic cancer comprising administering to a subject having pancreatic cancer a therapeutically effective amount of a combination comprising an immunotherapy agent and a SYK inhibitor. In certain embodiments, the immunotherapy agent is an anti-PD-1 or anti-PD-L1 agent, such as an anti-PD-1 or anti-PD-L1 antibody. In certain embodiments, the immunotherapy agent is selected from pembrolizumab and nivolumab. In certain embodiments, the immunotherapy agent is pembrolizumab. In certain embodiments, the immunotherapy agent is nivolumab. In certain embodiments, the SYK inhibitor is a compound of Formula I, Formula II, or Formula III. In certain embodiments, the SYK inhibitor is a compound of Formula II or a pharmaceutically acceptable salt thereof. In certain embodiments, the SYK inhibitor is a compound of Formula III or a crystalline form thereof.

[077] In certain embodiments, the cancer is colorectal cancer. In certain embodiments, the invention relates to a method for treating colorectal cancer comprising administering to a subject having colorectal cancer a therapeutically effective amount of a combination comprising an

immunotherapy agent and a SYK inhibitor. In certain embodiments, the immunotherapy agent is an anti-PD-1 or anti-PD-L1 agent, such as an anti-PD-1 or anti-PD-L1 antibody. In certain embodiments, the immunotherapy agent is selected from pembrolizumab and nivolumab. In certain embodiments, the immunotherapy agent is pembrolizumab. In certain embodiments, the immunotherapy agent is nivolumab. In certain embodiments, the SYK inhibitor is a compound of Formula I, Formula II, or Formula III. In certain embodiments, the SYK inhibitor is a compound of Formula II or a pharmaceutically acceptable salt thereof. In certain embodiments, the SYK inhibitor is a compound of Formula III or a crystalline form thereof.

[078] In certain embodiments, the cancer is ovarian cancer. In certain embodiments, the invention relates to a method for treating ovarian cancer comprising administering to a subject having ovarian cancer a therapeutically effective amount of a combination comprising an immunotherapy agent and a SYK inhibitor. In certain embodiments, the immunotherapy agent is an anti-PD-1 or anti-PD-L1 agent, such as an anti-PD-1 or anti-PD-L1 antibody. In certain embodiments, the immunotherapy agent is selected from pembrolizumab and nivolumab. In certain embodiments, the immunotherapy agent is pembrolizumab. In certain embodiments, the immunotherapy agent is nivolumab. In certain embodiments, the SYK inhibitor is a compound of Formula I, Formula II, or Formula III. In certain embodiments, the SYK inhibitor is a compound of Formula II or a pharmaceutically acceptable salt thereof. In certain embodiments, the SYK inhibitor is a compound of Formula III or a crystalline form thereof.

[079] In certain embodiments, the cancer is gastric cancer. In certain embodiments, the gastric cancer is gastroesophageal adenocarcinoma. In certain embodiments, the invention relates to a method for treating gastric cancer (e.g., gastroesophageal adenocarcinoma) comprising administering to a subject having gastric cancer a therapeutically effective amount of a combination comprising an immunotherapy agent and a SYK inhibitor. In certain embodiments, the immunotherapy agent is an anti-PD-1 or anti-PD-L1 agent, such as an anti-PD-1 or anti-PD-L1 antibody. In certain embodiments, the immunotherapy agent is selected from pembrolizumab and nivolumab. In certain embodiments, the immunotherapy agent is pembrolizumab. In certain embodiments, the immunotherapy agent is nivolumab. In certain embodiments, the SYK inhibitor is a compound of Formula I, Formula II, or Formula III. In certain embodiments, the SYK inhibitor is a compound of Formula II or a pharmaceutically acceptable salt thereof. In certain embodiments, the SYK inhibitor is a compound of Formula III or a crystalline form thereof.

[080] In certain embodiments, the cancer is endometrial cancer. In certain embodiments, the invention relates to a method for treating endometrial cancer comprising administering to a subject having endometrial cancer a therapeutically effective amount of a combination comprising an immunotherapy agent and a SYK inhibitor. In certain embodiments, the immunotherapy agent is an anti-PD-1 or anti-PD-L1 agent, such as an anti-PD-1 or anti-PD-L1 antibody. In certain embodiments, the immunotherapy agent is selected from pembrolizumab and nivolumab. In certain embodiments, the immunotherapy agent is pembrolizumab. In certain embodiments, the immunotherapy agent is nivolumab. In certain embodiments, the SYK inhibitor is a compound of Formula I, Formula II, or Formula III. In certain embodiments, the SYK inhibitor is a compound of Formula II or a pharmaceutically acceptable salt thereof. In certain embodiments, the SYK inhibitor is a compound of Formula III or a crystalline form thereof.

[081] In certain embodiments, the cancer is prostate cancer. In certain embodiments, the invention relates to a method for treating prostate cancer comprising administering to a subject having prostate cancer a therapeutically effective amount of a combination comprising an immunotherapy agent and a SYK inhibitor. In certain embodiments, the immunotherapy agent is an anti-PD-1 or anti-PD-L1 agent, such as an anti-PD-1 or anti-PD-L1 antibody. In certain embodiments, the immunotherapy agent is selected from pembrolizumab and nivolumab. In certain embodiments, the immunotherapy agent is pembrolizumab. In certain embodiments, the immunotherapy agent is nivolumab. In certain embodiments, the SYK inhibitor is a compound of Formula I, Formula II, or Formula III. In certain embodiments, the SYK inhibitor is a compound of Formula II or a pharmaceutically acceptable salt thereof. In certain embodiments, the SYK inhibitor is a compound of Formula III or a crystalline form thereof.

[082] In certain embodiments, the cancer is selected from brain and spine cancer, fallopian tube cancer, uterine cancer, bladder cancer, esophageal cancer, biliary tract cancer, urothelial cancer, soft tissue cancer, rectal cancer, thyroid cancer, bone cancer, salivary gland cancer, nasal cavity and paranasal sinus cancer, testicular cancer, adrenocortical cancer, thymic cancer, eye cancer, and gallbladder cancer. In certain embodiments, the invention relates to a method for treating cancer selected from brain and spine cancer, fallopian tube cancer, uterine cancer, bladder cancer, esophageal cancer, biliary tract cancer, urothelial cancer, soft tissue cancer, rectal cancer, thyroid cancer, bone cancer, salivary gland cancer, nasal cavity and paranasal sinus cancer, testicular cancer, adrenocortical cancer, thymic cancer, eye cancer, and gallbladder cancer comprising administering to a subject having cancer selected from brain and spine cancer, fallopian tube cancer, uterine

cancer, bladder cancer, esophageal cancer, biliary tract cancer, urothelial cancer, soft tissue cancer, rectal cancer, thyroid cancer, bone cancer, salivary gland cancer, nasal cavity and paranasal sinus cancer, testicular cancer, adrenocortical cancer, thymic cancer, eye cancer, and gallbladder cancer a therapeutically effective amount of a combination comprising an immunotherapy agent and a SYK inhibitor. In certain embodiments, the immunotherapy agent is an anti-PD-1 or anti-PD-L1 agent, such as an anti-PD-1 or anti-PD-L1 antibody. In certain embodiments, the immunotherapy agent is selected from pembrolizumab and nivolumab. In certain embodiments, the immunotherapy agent is pembrolizumab. In certain embodiments, the immunotherapy agent is nivolumab. In certain embodiments, the SYK inhibitor is a compound of Formula I, Formula II, or Formula III. In certain embodiments, the SYK inhibitor is a compound of Formula II or a pharmaceutically acceptable salt thereof. In certain embodiments, the SYK inhibitor is a compound of Formula III or a crystalline form thereof.

[083] In certain embodiments, the invention relates to a method of suppressing tumor regrowth, comprising administering a therapeutically effective amount of a combination comprising an immunotherapy agent and a SYK inhibitor. In certain embodiments, the immunotherapy agent is an anti-PD-1 or anti-PD-L1 agent, such as an anti-PD-1 or anti-PD-L1 antibody. In certain embodiments, the immunotherapy agent is selected from pembrolizumab and nivolumab. In certain embodiments, the immunotherapy agent is pembrolizumab. In certain embodiments, the immunotherapy agent is nivolumab. In certain embodiments, the SYK inhibitor is a compound of Formula I, Formula II, or Formula III. In certain embodiments, the SYK inhibitor is a compound of Formula II or a pharmaceutically acceptable salt thereof. In certain embodiments, the SYK inhibitor is a compound of Formula III or a crystalline form thereof.

[084] In certain embodiments, the growth of cells contacted with an immunotherapy agent and a SYK inhibitor is retarded by at least about 50% as compared to growth of non-contacted cells. In certain embodiments, cell proliferation of contacted cells is inhibited by at least about 75%, at least about 90%, or at least about 95% as compared to non-contacted cells. In certain embodiments, the phrase “inhibiting cell proliferation” includes a reduction in the number of contacted cells, as compare to non-contacted cells. In certain embodiments, an immunotherapy agent and an inhibitor of SYK that inhibits cell proliferation in a contacted cell may induce the contacted cell to undergo growth retardation, to undergo growth arrest, to undergo programmed cell death (i.e., apoptosis), or to undergo necrotic cell death.

[085] In certain embodiments, the immunotherapy agent and SYK inhibitor are administered such that they provide a synergistic effect in the treatment of a neoplastic disease. In certain embodiments, the immunotherapy agent and/or the SYK inhibitor may be administered in a sub-therapeutic amount. In certain embodiments, the immunotherapy agent and SYK inhibitor are administered such that they provide an additive effect in the treatment of a neoplastic disease.

[086] In certain embodiments, the immunotherapy agent and the SYK inhibitor are administered simultaneously, wherein simultaneous administration may comprise the two agents in a single formulation or may comprise the two agents in separate formulations. In certain embodiments, the immunotherapy agent and the SYK inhibitor are administered sequentially. In certain embodiments, the immunotherapy agent is administered prior to the SYK inhibitor. In certain embodiments, the SYK inhibitor is administered prior to the immunotherapy agent.

[087] In certain embodiments, the SYK inhibitor is administered orally and the immunotherapy agent is administered intravenously. In certain embodiments, the SYK inhibitor is administered intravenously and the immunotherapy agent is administered orally. In certain embodiments, the SYK inhibitor and the immunotherapy agent are both administered orally. In certain embodiments, the SYK inhibitor and the immunotherapy agent are both administered intravenously.

[088] The amounts or suitable doses of the selective inhibitor of SYK depends upon a number of factors, including the nature of the severity of the condition to be treated, the particular inhibitor, the route of administration and the age, weight, general health, and response of the individual subject. In certain embodiments, the suitable dose level is one that achieves an effective exposure as measured by increased skin mitotic index, or decreased chromosome alignment and spindle bipolarity in tumor mitotic cells, or other standard measures of effective exposure in cancer patients. In certain embodiments, the suitable dose level is one that achieves a therapeutic response as measured by tumor regression, or other standard measures of disease progression, progression free survival or overall survival. In certain embodiments, the suitable dose level is one that achieves this therapeutic response and also minimizes any side effects associated with the administration of the therapeutic agent.

[089] In certain embodiments, the SYK inhibitor is administered daily. Suitable daily dosages of a SYK inhibitor of Formula I, II, or III can generally range, in single or divided or multiple doses, from about 20 mg to about 150 mg per day or about 40 mg to about 120 mg. In certain embodiments, suitable daily doses are about 20 mg, 30 mg, about 30 mg, about 40 mg, 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about

130 mg, or about 140 mg or about 150 mg per day. In certain embodiments, the suitable dose may be given once daily or may be divided such that the compound is given twice or three times daily. In certain embodiments, the daily dose of the SYK inhibitor is about 20 mg. In certain embodiments, the daily dose of the SYK inhibitor is about 30 mg. In certain embodiments, the daily dose of the SYK inhibitor is about 40 mg. In certain embodiments, the daily dose of the SYK inhibitor is about 60 mg. In certain embodiments, the daily dose of the SYK inhibitor is about 80 mg. In certain embodiments, the daily dose of the SYK inhibitor is about 100 mg. In certain embodiments, the daily dose of the SYK inhibitor is about 120 mg. In certain embodiments, the daily dose of the SYK inhibitor is about 150 mg. In certain embodiments, the SYK inhibitor is administered once daily. In certain embodiments, the SYK inhibitor is administered orally, once daily.

[090] In certain embodiments, the immunotherapy agent is administered once every two weeks or once every three weeks. In certain embodiments, the immunotherapy agent is administered once every two weeks. In certain embodiments, the immunotherapy agent is administered once every three weeks. In certain embodiments, the immunotherapy agent is administered once every four weeks. In another embodiment, the immunotherapy agent is dosed according to a weight-based dosing, e.g., mg/kg. In another embodiment, the immunotherapy agent is administered as a fixed dose, e.g., mg per dose. Suitable doses of an immunotherapy agent can generally range from about 1 mg/kg to about 4 mg/kg or about 2 mg/kg to about 3 mg/kg. In certain embodiments a suitable dose of the immunotherapy agent is 2 mg/kg. In certain embodiments, a suitable dose of the immunotherapy agent is 3 mg/kg. In certain embodiments, a suitable dose of the immunotherapy agent is from about 200 mg to about 300 mg. In certain embodiments, a suitable dose of the immunotherapy agent is 240 mg. In certain embodiments, the immunotherapy agent is nivolumab administered at a dose of 3 mg/kg every 2 weeks, such as on days 1 and 15 of a 28 day cycle. In certain embodiments, the immunotherapy agent is nivolumab administered at a dose of 240 mg every two weeks, such as on day 1 and 15 of a 28-day cycle. In certain embodiments, nivolumab is administered once every two weeks at about 240 mg dose. In certain embodiments, nivolumab is administered once every two weeks on day 1 and 15 of a 28-day cycle at about 240 mg dose. In certain embodiments, the immunotherapy agent is pembrolizumab administered at a dose of 2 mg/kg every 3 weeks, such as on days 1 and 22 of a 28 day cycle. In certain embodiments, the immunotherapy agent is administered intravenously. In certain embodiments, the immunotherapy agent is administered according to local guidelines. In certain embodiments, the immunotherapy agent is administered according to the product insert or the summary of product characteristic for the immunotherapy agent. In certain embodiments, nivolumab is administered according to its U.S.

product insert or summary of product characteristics. See, e.g., OPDIVO (nivolumab) [prescribing information], Princeton, NJ: Bristol-Myers Squibb, 2016, available at http://packageinserts.bms.com/pi/pi_opdivo.pdf; OPDIVO 10 mg/mL concentrate for solution for infusion (nivolumab) [summary of product characteristics], available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003985/WC500189765.pdf.

[091] The therapeutically effective amount of the subject combination of compounds may vary depending upon the intended application (*in vitro* or *in vivo*), or the subject and disease condition being treated, e.g., the weight and age of the subject, the severity of the disease condition, the manner of administration and the like. The term also applies to a dose that will induce a particular response in target cells, e.g., reduction of proliferation or downregulation of activity of a target protein. The specific dose will vary depending on the particular compounds chosen, the dosing regimen to be followed, whether it is administered in combination with other compounds, timing of administration, the tissue to which it is administered, and the physical delivery system in which it is carried.

[092] The amounts or suitable doses of the methods of this disclosure depends upon a number of factors, including the nature of the severity of the condition to be treated, the particular inhibitor, the route of administration and the age, weight, general health, and response of the individual subject. In certain embodiments, the suitable dose level is one that achieves a therapeutic response as measured by tumor regression, or other standard measures of disease progression, progression free survival or overall survival. In certain embodiments, the suitable dose level is one that achieves this therapeutic response and also minimizes any side effects associated with the administration of the therapeutic agent. The suitable dose levels may be ones that prolong the therapeutic response and/or prolong life.

[093] It will be understood that a suitable dose of the immunotherapy agent and the SYK inhibitor may be taken at any time of the day or night. In certain embodiments, a suitable dose of each therapeutic agent is taken in the morning. In certain embodiments, a suitable dose of each therapeutic agent is taken in the evening. In certain embodiments, a suitable dose of each of the therapeutic agents is taken both in the morning and the evening. It will be understood that a suitable dose of each inhibitor may be taken with or without food. In certain embodiments a suitable dose of a therapeutic agent is taken with a meal. In certain embodiments a suitable dose of a therapeutic agent is taken while fasting.

Pharmaceutical Compositions

[094] In certain embodiments, the SYK inhibitor and the immunotherapy agent are both administered orally such as in a solid dosage form or a liquid dosage form. In certain embodiments, the immunotherapy agent inhibitor is administered as a solid dosage form. In certain embodiments, the immunotherapy agent is administered as a liquid dosage form. In certain embodiments, the SYK inhibitor is administered as a solid dosage form. In certain embodiments, the SYK inhibitor is administered as a liquid dosage form.

[095] In certain embodiments, solid dosage forms for oral administration are capsules, tablets, pills, powders, and granules. In certain embodiments, in such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or (a) fillers or extenders such as, for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, (c) humectants such as, for example, glycerol, (d) disintegrating agents such as, for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, (e) solution retarding agents such as paraffin, (f) absorption accelerators such as, for example, quaternary ammonium compounds, (g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, (h) absorbents such as, for example, kaolin and bentonite clay, and (i) lubricants such as, for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In certain embodiments, capsules, tablets and pills may also comprise buffering agents such as phosphates or carbonates.

[096] In certain embodiments, solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. In certain embodiments, the solid dosage forms of tablets, dragees, capsules, pills, and granules may be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also optionally be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. In certain embodiments, solid dosage forms may be embedding compositions that may comprise polymeric substances and waxes.

[097] In certain embodiments, liquid dosage forms for oral administration are pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In certain embodiments, in addition to the active compounds, the liquid dosage forms may contain inert

diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, cyclodextrins, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. In certain embodiments, besides inert diluents, the oral compositions can also include adjuvants such as, for example, wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Medical kits

[098] The present disclosure also provides medical kits. In certain embodiments, the kits comprise an immunotherapy agent and an SYK inhibitor as described herein. In certain embodiments, the kits comprise an immunotherapy agent and an SYK inhibitor as described herein, in suitable packaging, and written materials that can comprise instructions for use, discussion of clinical studies, listing of side effects, and the like. In certain embodiments, such kits may also comprise information, such as, for example, scientific literature references, package insert materials, clinical trial results, and/or summaries of these and the like, which indicate or establish the activities and/or advantages of the composition, and/or which describe dosing, administration, side effects, drug interactions, or other information useful to the health care provider. In certain embodiments, such information may be based on the results of various studies, for example, studies using experimental animals involving in vivo models and studies based on human clinical trials. In certain embodiments, the kit may further comprise another agent. In certain embodiments, the SYK inhibitor of the present disclosure and the immunotherapy agent are provided as separate compositions in separate containers within the kit. In certain embodiments, the SYK inhibitor of the present disclosure and the immunotherapy agent are provided as a single composition within a container in the kit. Suitable packaging and additional articles for use (e.g., measuring cup for liquid preparations, foil wrapping to minimize exposure to air, and the like) are known in the art and may be included in the kit. Kits described herein can be provided, marketed and/or promoted to health providers, including physicians, nurses, pharmacists, formulary officials, and the like. Kits may also, in some embodiments, be marketed directly to the consumer.

Further Combination therapies

[099] The present invention also provides methods for further combination therapies in which, in addition to an immunotherapy agent and an SYK inhibitor, one or more agents known to modulate other pathways, or the same pathway, may be used. In certain embodiments, such therapy includes

but is not limited to the combination of the composition comprising at least one immunotherapy agent and at least one SYK inhibitor, as described herein, with one or more additional therapeutic agents such as anticancer agents, chemotherapeutic agents, therapeutic antibodies, and radiation treatment, to provide, where desired, a synergistic or additive therapeutic effect. In certain embodiments, pathways that may be targeted by administering another agent include, but are not limited to, spleen tyrosine kinase (SYK), MAP kinase, Raf kinases, Akt, NFkB, WNT, RAS/RAF/MEK/ERK, JNK/SAPK, p38 MAPK, Src Family Kinases, JAK/STAT and/or PKC signaling pathways. In some embodiments, other agents may target one or more members of one or more signaling pathways. Representative members of the nuclear factor-kappaB (NFkB) pathway include but are not limited to RelA (p65), RelB, c-Rel, p50/p105 (NF-κB 1), p52/p 100 (NF-κB2), IκB, and IκB kinase. Non-limiting examples of receptor tyrosine kinases that are members of the phosphatidylinositol 3-kinase (PI3K)/AKT pathway that may be targeted by one or more agents include FLT3 LIGAND, EGFR, IGF-1R, HER2/neu, VEGFR, and PDGFR. Downstream members of the PI3K/AKT pathway that may be targeted by agents according to the methods of the invention include, but are not limited to, forkhead box O transcription factors, Bad, GSK-3β, I-κB, mTOR, MDM-2, and S6 ribosomal subunit.

Examples

Example 1: *In vivo* CT26 mouse syngeneic colon cancer model.

[0100] Animals: Balb/c mice from JAX (approximately 20 grams body weight, female) were used. They were group-housed and provided food and water ad libitum prior to the experiment. Mice were maintained on a 12-hour light and dark cycle and maintained in the vivarium for at least 7 days after receipt prior to investigations.

[0101] Drugs used in this study: Compound A (10, 30, and 60 mg/kg, formulated in 0.5% Methocel at 1, 3, and 6 mg/mL, dosed at 10 mL/kg, oral administration (PO)). Anti-PD-1 monoclonal antibody (Anti-PD-1) (BioXcell, RMP1-14, formulated in 0.9% saline at 2 mg/ml, dosed at 5 mL/kg, intraperitoneal administration (IP) for final dose of 10 mg/kg).

[0102] Cell Culture: CT26 cells (ATCC CRL-2638) were cultured in RPMI-1640 containing 10% FBS and pen/strep. Media was changed every 2-3 days and cells were split at ~80% confluence. A maximum of 20 passages were allowed prior to re-initiating the culture from the original cell stock.

[0103] *In vivo* CT26 syngeneic model: Day -2 prior to tumor injection, the fur of each animal was shaved from the rump up to the middle of the back and extends to the flank on each side. At day 0, CT26 cells were suspended in cold RPMI1640 media and Matrigel (1:1) to final cell concentration

of 2×10^6 /ml and injected 0.1mL (0.2×10^6 cells/mouse) subcutaneously in the flank. At Day 7 after inoculation, animals were sorted and randomized into 8 groups and treatment was initiated as illustrated in Table 1. Tumor size was measured by caliper (width x length) and body weights were recorded twice a week until day 21. Tumor volumes were calculated using the formula $TV = (\text{width}^2 \times \text{length}) \times 0.52$ and tumor growth inhibition (TGI) was calculated using the formula $(\text{Vehicle} - \text{Treatment})/\text{Vehicle} \times 100$ at each time point. Statistical significance was assessed by one-way ANOVA followed by Dunnett's post-test, comparing all groups versus vehicle (GraphPad Prism, GraphPad Software, Inc., La Jolla, CA, USA).

Table 1.

Group	Treatment	Dose (mg/kg)	Frequency ¹	Route	N
1	Non-treated	-	-	-	10
2	Compound A	10	QD Days 7-21	PO	10
3	Compound A	30	QD Days 7-21	PO	10
4	Compound A	60	QD Days 7-21	PO	10
5	Anti-PD-1	10	Days 7, 9, 13, 15, 18	IP	10
6	Compound A + Anti-PD-1	10 + 10	QD Days 7-21 + Days 7, 9, 13, 15, 18	PO + IP	10
7	Compound A + Anti-PD-1	30 + 10	QD Days 7-21 + Days 7, 9, 13, 15, 18	PO + IP	10
8	Compound A + Anti-PD-1	60 + 10	QD Days 7-21 + Days 7, 9, 13, 15, 18	PO + IP	10

¹QD is once daily administration.

[0104] Results: Results are expressed as mean $\pm$ standard error of the mean (SEM). A probability level of $p < 0.05$ was considered statistically significant. Results are shown in Figure 1 and Table 2 below. Briefly, Compound A monotherapy demonstrated TGI of 13, 17.3, and 38.3% at 10, 30, and 60 mg/kg, respectively and Compound A combination therapy demonstrated TGI of 3.6, 58.5, 70.1% at 10, 30, and 60 mg/kg, respectively. Compound A showed a protective effect on body weight loss at 60 mg/kg monotherapy and at doses of 30 and 60 mg/kg in combination therapy. Compound A at 60 mg/kg monotherapy produced survival of 30% at Day 35 and Compound A in combination therapy produced survival of 60 and 80% at Day 35 for 30 and 60 mg/kg, respectively.

Table 2.

Group	Mean Tumor Volume at Day 20 ± S.E.M (mm ³) ¹	TGI (%)	% Body Weight Change mean ± S.E.M		Percent Survival		
			Day 17	Day 20	Day 21	Day 28	Day 35
Non-treated	562.3 ± 63.4	-	1 ± 2.1	-5.7 ± 4.3	70	10	0
Compound A, 10 mg/kg	489.4 ± 29.1	13	2.8 ± 1.3	-8.3 ± 3.6	100	0	0
Compound A, 30 mg/kg	465.3 ± 57.1	17.3	0.7 ± 1.4	-2.6 ± 3.3	100	20	20
Compound A, 60 mg/kg	346.8 ± 60.2	38.3	4.6 ± 2.9	4.6 ± 3.9	100	60	30
Anti-PD-1	372.8 ± 99.6	33.7	-0.3 ± 2.1	-3.3 ± 3.3	80	30	30
Compound A, 10 mg/kg + Anti-PD-1	542 ± 51.7	3.6	-1.1 ± 2.6	-9.9 ± 3.4	70	10	0
Compound A, 30 mg/kg + Anti-PD-1	233.1 ± 61.3 ²	58.5	1.2 ± 2.3	2.5 ± 4.1	100	70	60
Compound A, 60 mg/kg + Anti-PD-1	167.9 ± 71.4 ³	70.1	1.9 ± 0.7	4.0 ± 0.9	100	90	80

¹One-way ANOVA with Dunnett post-test. ²p<0.01. ³p<0.001.

[0105] In addition to the results shown in Figure 1 and Table 2, 80% of the animals treated with Compound A (60 mg/kg) in combination with Anti-PD-1 were tumor free, even 30 days after the last dose was administered. This shows that the combination resulted in a complete cure for a prolonged period of time. In comparison, only 20% of animals treated with Compound A alone survived to 30 days after the last dose, and only 30% of animals treated with anti PD-1 antibody alone survived to 30 days after the last dose. See Figure 2.

[0106] Figure 3 and Figure 4 show that Compound A, either alone or in combination with anti PD-1 antibody resulted in decrease in percentage of B-cells (B220 +cells) and myeloid-derived suppressor cells (MDSCs) (CD11b+ cells). This suggests that Compound A impacts B-cells and MDSCs in the tumor milieu.

Example 2: *In vivo* 4T1 mouse syngeneic breast cancer model.

[0107] The objective of the study was to evaluate the antitumor activity of Compound A alone or Compound A in combination with the mouse Anti-PD-1 antibody in a syngeneic mouse model of 4T1 breast cancer.

[0108] 1×10^5 of 4T1 tumor cells (cell suspension) were injected to mammary fat pad (in the flank) to Balb/C mice (Charles River; weight at treatment start 19.5g). Tumor growth was monitored with vernier calipers. The tumor volume was calculated using the formula $V = W^2 \times L / 2$, where V = volume, W = width, and L = length of the tumor. The treatment started when the tumors reached a mean volume of approximately 80 mm^3 . The animals were randomized into treatment groups ($n=5/\text{group}$) and dosed with 0.5% Methylcellulose, Compound A, or Anti-PD-1.

[0109] Compound A at 60 mg/kg was administered daily (QD) PO for 21 consecutive days. Anti-PD-1 at 10 mg/kg was administered every 4 days (Q4D) IP for 3 doses in total. Compound A at 60 mg/kg combined with Anti-PD-1 at 10 mg/kg was administered following the same dosing regimen as the single agents. Administration route, schedule, and duration for this study are summarized in Table 3.

[0110] During the treatment period from Day 0 to Day 21, no mortality or body weight loss (BWL) was observed in the present study. No mice were removed from the study during the treatment period.

[0111] Tumor growth and body weight were measured twice per week. Tumor growth inhibition and body weight change were calculated on Day 19 of treatment.

[0112] The differences in the tumor growth trends over time between pairs of treatment groups were assessed using linear mixed effects regression models. These models account for the fact that each animal was measured at multiple time points. A separate model was fit for each comparison, and the areas under the tumor volume versus time curve (AUC) for each treatment group were calculated using the predicted values from the model. The percent decrease in AUC (dAUC) relative to the reference group was then calculated. A statistically significant P value suggests that the trends over time for the two treatment groups were different.

[0113] The results of the pairwise comparison to vehicle showed that the daily administration of Compound A alone at 60 mg/kg resulted in 29.6% (ΔAUC , $p=0.02$) tumor growth inhibition (TGI) value on Day 19. Anti-PD-1 alone at 10 mg/kg resulted in TGI value of -17.9% (ΔAUC , $p=0.518$) on Day 19. Compound A at 60 mg/kg combined with Anti-PD-1 at 10 mg/kg had 8.4% (ΔAUC , $p=$

0.717) TGI value on Day 19. All TGI calculations were completed on Day 19 due to the faster tumor growth rate.

[0114] The antitumor activities of Compound A, Anti-PD-1, and combination of Compound A with Anti-PD-1 against 4T1 breast cancer model are summarized in Table 3 and graphically presented in Figure 5.

Table 3.

Test Article	Dose (mg/kg)	Route Schedule Duration	% BW ^a Change (Day Maximum)	Mean Tumor Volume (mm ³) ± SEM ^b	T/C	TGI ^c (%)	P-Value ^d (dAUC)
					Day 19		
0.5% Methyl-cellulose	N/A	PO QD 21	12.2 (19)	1,529.3 ± 58.5	N/A	N/A	N/A
Compound A	60.0	PO QD 21	9.2 (19)	1,076 ± 113.2	0.70	29.6	0.02
Anti-PD-1	10.0	IP Q4Dx3 21	20.5 (14)	1,803.2 ± 197.3	1.18	-17.9	0.518
Compound A + Anti-PD-1 ^e	60.0 + 10.0	PO QD 21; IP Q4Dx3 21	13.9 (14)	1,401.5 ± 52.4	0.92	8.4	0.717

TGI and T/C values were calculated on Day 19 of treatment.

^a % Body weight change (Day of Maximum change within the treatment period).

^b Standard error of the mean.

^c TGI = 100 – [(treated average volume / control average volume) x 100].

^d The changes in the areas under the tumor volume versus time curves (ΔAUCs) were assessed using linear mixed effects regression models to compare treatment groups with vehicle. P-values <0.05 indicate the percent decrease in AUC (dAUC) relative to the reference group was statistically significant.

^eSequencing: Compound A//Anti-PD-1 (Compound A was administered first).

Example 3: Clinical solid tumor study design — a study of Compound A in combination with nivolumab in subjects with advanced solid tumors.

[0115] Recent studies have shown that myeloid-derived suppressor cells (MDSCs) use CD79-ITAM signaling that uses SYK as a signaling mediator. Additionally, Fms-like tyrosine kinase 3 (FLT3) and its ligand have been shown to induce MDSCs in vitro. LECHNER et al., J. Transl. Med. 9:90 (2011).

[0116] MDSC-mediated immune suppression has been reported in many solid tumors, including, but not limited to breast cancer, head and neck, and NSCLC. COTECHINI et al., *Cancer. J.*, 21(4): 343-50 (2015). In addition, a role of B cells in tumor immunity has been studied, and the requirement of B cells for tumor growth and metastasis has been documented. DILILLO et al., *J. Immunol.*, 184(7):4006-4016 (2010). SYK is known to be essential for development, growth, and maintenance of B cells.

[0117] SYK inhibition results in the loss of MDSCs and activation of T-cell response, both in vitro and in vivo. See, e.g., LUGER et al., *PLoS One*, 8(10):e76115 (2013). Although preclinical experiments in tumors in which SYK-mediated MDSC or B-cell immunosuppression are active show that Compound A did not inhibit or activate T cells directly, in certain embodiments, synergistic activity may be observed when a PD-1 receptor inhibitor that promotes T-cell function is administered in combination with a SYK inhibitor. The benefit of administering an anti-PD-1 agent with Compound A has been observed nonclinically, as in Example 1, and this effect may be indirectly attributed to the decrease in CD11b⁺ MDSC or B220⁺ B cells in the tumor-infiltrating immune cells of Compound A-treated tumors.

[0118] Accordingly, the addition of a SYK inhibitor, such as Compound A, to an anti-PD-1 agent may improve tumor regression via modulation of the tumor-infiltrating immune cells and other immune cells in the tumor microenvironment. The make-up of the tumor microenvironment, which differs among different tumor types, informs the choice of diseases to be evaluated in this study. Tumors in which there is MDSC or B-cell suppression are of particular interest: nonclinical assessment suggests that tumors such as TNBC, NSCLC, and HNSCC show MDSC-mediated tumor immunosuppression.

[0119] The study intends to clinically evaluate the combination effect of Compound A and nivolumab in 3 advanced solid tumor types (TNBC, NSCLC, and HNSCC). With the reference response rate of ~20% observed with nivolumab monotherapy in each of these indications, added benefit of this combination regimen will be assessed by whether a significantly improved overall response rate (ORR; target ORR of 40%) is observed, along with assessment of other efficacy measures such as duration of response (DOR) and survival benefit. While the majority of the subjects in each of the cohorts (24/30 response-evaluable subjects) should be naïve to anti-PD-1, anti-PD-L1, and any other immune-directed antitumor therapies, a small subset of 6/30 response-evaluable subjects with prior exposure to an anti-PD-1 or anti-PD-L1 agent will be enrolled to observe any combination effect of Compound A plus nivolumab in this relapsed/refractory setting with regard to the PD-1/PD-L1 blockade. In addition, after determining a safe and tolerable

combination dose for Compound A when co-administered with nivolumab during the initial dose escalation stage of the study, a 2-week, single-agent Compound A treatment period before combination therapy is planned in 10 response-evaluable subjects in each of the expansion cohorts. Correlative science studies are planned in pretreatment and post-treatment tumor biopsies and peripheral blood samples taken from these subjects with the intent of having more mechanistic understanding of the role of SYK in the tumor immunity and direct tumor effect, if any.

[0120] This is an open-label, multicenter, phase 1b, dose escalation study of Compound A in combination with nivolumab in subjects with advanced solid tumors. The purpose of this study is to evaluate the maximum tolerated dose (MTD) or recommended Part 2 dose (RP2D), safety and efficacy of Compound A in combination with nivolumab in subjects with advanced solid tumors.

[0121] The drug being tested is Compound A. This study will look at the determination of MTD/RP2D and efficacy measured by overall response rate (ORR) in subjects who take Compound A in combination with nivolumab. The study will include a dose escalation phase (Part 1) and a dose expansion phase (Part 2).

[0122] All subjects will be asked to take the tablets of Compound A at the same time each day throughout the study. Subjects will also receive intravenous infusion of nivolumab at the same time once every 2 weeks. This multi-center trial will be conducted globally. The overall time to receive treatment in this study is approximately 12 months. Subjects will be assessed for disease response and PD during the progression-free survival (PFS) follow-up of 6 months (for subjects who discontinue due to reasons other than PD) and OS follow-up of 12 months from the last dose of study drug.

[0123] The study will include a dose escalation phase (Part 1) and a dose expansion phase (Part 2). In the dose escalation phase, the subject population will consist of all-comer subjects with advanced solid tumors for whom 1 or more prior lines of therapy have failed and who have no effective therapeutic options available based on investigator assessment. The dose expansion phase will include 3 cohorts: (1) subjects with metastatic triple-negative breast cancer (TNBC) who have had ≥ 1 prior line of chemotherapy; (2) subjects with locally advanced or metastatic non-small cell lung cancer (NSCLC) that has progressed on or after a prior platinum-based chemotherapy; and (3) subjects with locally advanced or metastatic head and neck squamous cell carcinoma (HNSCC) that has progressed or recurred within 6 months of the last platinum-based chemotherapy.

[0124] It is expected that approximately 120 subjects will be enrolled in the study: approximately 9 to 12 subjects in the dose escalation cohort and approximately 36 subjects (30 evaluable subjects + 15% drop off) in each of the 3 dose expansion cohorts. Subjects will be assigned to 1 of the 4 treatment groups: Part 1 Compound A + Nivolumab; Part 2 Metastatic TNBC; Part 2 Metastatic NSCLC; and Part 2 Metastatic HNSCC.

[0125] Once enrolled in the study, subjects will be administered Compound A orally once daily during each 28-day treatment cycle. Subjects receiving the combination therapy will also receive nivolumab once every 2 weeks intravenously (IV) over 60 minutes on Day 1 and Day 15 of each 28-day treatment cycle (for subjects who receive 2 weeks of Compound A monotherapy before starting combination treatment, the first nivolumab infusion will be administered on Cycle 1 Day 15). On days when both Compound A and nivolumab will be administered, the Compound A dose will be administered first followed by the nivolumab infusion (infusion to begin within 30 minutes after the Compound A dose). Subjects, including those who achieve a complete response, may receive study treatment until they experience disease progression (PD) or unacceptable toxicities.

[0126] The dose of nivolumab will be 3 mg/kg IV. The starting dose of Compound A will be 60 mg QD. Dose escalation will follow a standard 3+3 escalation scheme, and dosing will increase to 100 mg QD, provided that the safety and tolerability of the 60 mg dose has been demonstrated. Intermediate dose levels between 60 and 100 mg (e.g., 80 mg) or dose levels below the starting dose of 60 mg (e.g., 40 mg) may be also evaluated if appropriate. Dose escalation will continue until the maximum tolerated dose (MTD) is reached, or until 100 mg QD of Compound A (the maximally administered dose, (MAD)) is determined to be safe and tolerable, or until a recommended phase 2 dose (RP2D), if different from the MTD or MAD, has been identified on the basis of the safety, tolerability, and preliminary pharmacokinetic (PK) and efficacy data (if available) observed in Cycle 1 and beyond. At least 6 subjects will be evaluated at the RP2D (the MTD, MAD, or a lower dose as determined) before making a decision to advance to further dose expansion.

[0127] After the combination RP2D (the MTD, MAD, or a lower dose) is determined, expansion cohorts are planned in subjects with TNBC, NSCLC, and HNSCC. Thirty response-evaluable subjects will be enrolled in each expansion cohort, including approximately 10 subjects in each cohort who are able to provide evaluable serial biopsies. Additionally, each expansion cohort will include 24 response-evaluable subjects who are naïve to anti-PD-1/anti-PD-L1 therapy and 6 response-evaluable subjects who are relapsed/refractory to prior anti-PD-1/anti-PD-L1 therapy. Ten response-evaluable subjects in each expansion cohort will first receive single-agent treatment with

Compound A for 2 weeks at the RP2D previously determined in combination with nivolumab. Following the 2-week, single-agent treatment, Compound A treatment will continue (at the same dose) in combination with nivolumab during Week 3 and beyond.

[0128] The subset of expansion subjects who will be treated with single-agent Compound A at its combination RP2D during Weeks 1 and 2 should have accessible tumors for core or excisional biopsy and provide permission for the biopsies to be taken. These subjects will undergo mandatory biopsies before single-agent Compound A treatment begins, at the end of the 2-week treatment window, and after 6 weeks of treatment with Compound A in combination with nivolumab; an optional biopsy will also be taken at the time of PD. The biopsies will be used for biomarker analysis evaluating the effect of Compound A on tumor cells and on immune/stromal cells supporting tumor tissue.

[0129] The remaining 20 response-evaluable subjects in each expansion cohort will receive Compound A at its RP2D in combination with nivolumab, starting from Week 1, Day 1.

[0130] During dose escalation, serial blood samples for assessment of Compound A plasma PK will be collected for 24 hours after Compound A dosing on Cycle 1 Days 1 and 15, the days on which both Compound A and nivolumab are administered. Although the risk of drug-drug interaction between Compound A and nivolumab is predicted to be low, Compound A plasma PK following combination administration in the dose escalation will be compared with historical plasma PK following single-agent administration to confirm no clinically meaningful differences in Compound A PK between the single-agent and combination settings. For purposes of population PK analysis, sparse collection of PK samples will occur in the expansion cohorts during both the single-agent and combination administration periods.

[0131] All subjects in the expansion cohorts will be treated until either PD or occurrence of unacceptable toxicities. The objectives of these expansion cohorts are to evaluate efficacy of Compound A in combination with nivolumab as measured by overall response rate (ORR) and to determine the safety and tolerability of Compound A in combination with nivolumab.

[0132] Primary Objectives: (1) To determine the MTD/RP2D of Compound A when administered in combination with nivolumab (dose escalation). (2) To determine the efficacy of Compound A plus nivolumab as measured by ORR (dose expansion).

[0133] Secondary Objectives: (1) To determine the safety and tolerability of Compound A when administered in combination with nivolumab. (2) To evaluate other efficacy measures such as

disease control rate (response plus stable disease), duration of response (DOR), rate of PD at 6 months, progression-free survival (PFS), and overall survival (OS). (3) To characterize the plasma PK of Compound A when administered in combination with nivolumab.

Subject population:

[0134] Dose escalation: Subjects aged 18 years or older with advanced solid tumors for whom 1 or more prior lines of therapy have failed and who have no effective therapeutic options available based on investigator assessment. Dose expansion: Subjects aged 18 years or older with: (1) metastatic TNBC with ≥ 1 prior line of chemotherapy; (2) locally advanced or metastatic NSCLC that has progressed on or after a prior platinum-based chemotherapy; or (3) locally advanced or metastatic HNSCC that has progressed or recurred within 6 months of the last platinum-based chemotherapy.

Number of subjects:

[0135] It is expected that approximately 120 subjects will be enrolled in the study: approximately 9 to 12 subjects in the dose escalation cohort and approximately 36 subjects in each of the 3 dose expansion cohorts.

Dose level(s):

[0136] Compound A: oral daily dosing with 3+3 dose escalation planned at 60 and 100 mg. The RP2D determined in combination with nivolumab during dose escalation will be used for dose expansion cohorts. Nivolumab: 3 mg/kg IV dosing over 60 minutes every 2 weeks (Day 1 and Day 15 of each 28-day cycle). For subjects participating in the 2-week monotherapy run-in with Compound A, the first dose will be on Cycle 1 Day 15.

Duration of treatment:

[0137] Treatment will continue until disease progression (PD), unacceptable toxicities, or withdrawal due to other reasons. The estimated treatment duration is 12 months.

Route of administration:

[0138] Compound A: oral. Nivolumab: IV.

Period of evaluation:

[0139] PFS follow-up of 6 months (for subjects who discontinue due to reasons other than PD) and OS follow-up of 12 months from the last dose of study drug are planned.

Arms:

[0140] Part 1 Compound A + Nivolumab: Compound A 60 mg, tablets, orally, once daily in each 28-day treatment cycles in combination with nivolumab 3 milligram per kilogram (mg/kg), infusion, intravenously over 60 minutes, on Days 1 and 15 in each 28 days treatment cycles until PD or unacceptable toxicity. For subjects who will receive 2 weeks of Compound A monotherapy before starting combination treatment, the first nivolumab infusion will be administered on Cycle 1 Day 15. Dose escalation of Compound A to 100 mg may be done using a 3 + 3 dose escalation design to determine a maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D).

[0141] Part 2 Metastatic TNBC: Subjects with metastatic triple-negative breast cancer (TNBC) will receive Compound A at RP2D as determined in Part 1, tablets, orally, once daily in each 28-day treatment cycles in combination with nivolumab 3 mg/kg, infusion over 60 minutes, intravenously, once only on Day 15 of Cycle 1 (following first 2 week monotherapy of Compound A) and thereafter Days 1 and 15 in each 28 days treatment cycles until progressive disease or unacceptable toxicity.

[0142] Part 2 Metastatic NSCLC: Subjects with metastatic NSCLC will receive Compound A at RP2D as determined in Part 1, tablets, orally, once daily in each 28-day treatment cycles in combination with nivolumab 3 mg/kg, infusion over 60 minutes, intravenously, once only on Day 15 of Cycle 1 (following first 2 week monotherapy of Compound A) and thereafter Days 1 and 15 in each 28 days treatment cycles until progressive disease or unacceptable toxicity.

[0143] Part 2 Metastatic HNSCC: Subjects with metastatic HNSCC will receive Compound A at RP2D as determined in Part 1, tablets, orally, once daily in each 28-day treatment cycles in combination with nivolumab 3 mg/kg, infusion over 60 minutes, intravenously, once only on Day 15 of Cycle 1 (following first 2 week monotherapy of Compound A and thereafter Days 1 and 15 in each 28 days treatment cycles until progressive disease or unacceptable toxicity.

Criteria for inclusion:

[0144] (1) Is a male or female subjects aged 18 years or older.

[0145] (2) Has eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.

[0146] (3) Female subjects who: (a) are postmenopausal for at least 1 year before the screening visit, or (b) are surgically sterile, or (c) if childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent through 180 days after the last dose of study drug, or (d) agree to practice true abstinence, when this is in line with the

preferred and usual lifestyle of the subjects. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. Male subjects, even if surgically sterilized (i.e., status postvasectomy), who: (a) agree to practice effective barrier contraception during the entire study treatment period and through 180 days after the last dose of study drug, or (b) agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subjects. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods for the female partner) and withdrawal are not acceptable methods of contraception.

[0147] (4) Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the subjects at any time without prejudice to future medical care.

[0148] (5) Suitable venous access for the study-required blood sampling, including PK and pharmacodynamic sampling.

[0149] (6) Clinical laboratory values as specified below within 28 days before the first dose of study drug: (a) Total bilirubin must be less than equal to ($\leq$) 1.5*the upper limit of normal (ULN). (b) Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) must be $\leq$ 2.5*ULN. (c) Serum Creatinine must be $\leq$ 1.5*ULN or creatinine clearance or calculated creatinine clearance must be greater than ($>$) 50 milliliter per minute (mL/minute). (d) Hemoglobin must be greater than equal to ($\geq$) 8 gram per deciliter (g/dL), absolute neutrophil count (ANC) must be $\geq$ 1500 per microliter (/mCL), and platelet count must be $\geq$ 75,000/mCL.

[0150] (7) Recovered (i.e., $\leq$ Grade 1 toxicity) from the reversible effects of prior anticancer therapy.

[0151] (8) To be enrolled in the dose escalation phase of the study, subjects must have a radiographically or clinically evaluable tumor, but measurable disease as defined by RECIST version 1.1 is not required for participation in this study. EISENHAUER et al., Eur. J. Cancer, 45(2):228-247 (2009).

[0152] (9) To be enrolled in the TNBC expansion cohort, subjects must have: (a) Histologically confirmed, metastatic TNBC with measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. (b) Triple-negative disease (estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (HER 2) negativity) confirmed on a histological biopsy of a metastatic tumor lesion (receptor conversion not allowed). (c) Safely

accessible tumor lesions (based on investigator's assessment) for serial pretreatment and posttreatment biopsies are required for subjects receiving Compound A monotherapy run-in treatment for 2 weeks followed by Compound A plus nivolumab combination treatment (similar approximately 10/30 response-evaluable subjects); adequate, newly obtained, core or excisional biopsy of a metastatic tumor lesion not previously irradiated is required. Mandatory biopsies will be taken before Compound A monotherapy, after the 2 weeks of Compound A monotherapy, and after 6 weeks of Compound A plus nivolumab combination therapy. An optional biopsy may be taken at PD with additional consent from the subject. (d) One, two, or three line(s) of chemotherapy for metastatic disease and with progression of disease on last treatment regimen. For the purposes of this study, neoadjuvant and/or adjuvant chemotherapy regimens do not count as a prior line of therapy. Prior treatment must include an anthracycline and/or a taxane in the neoadjuvant, adjuvant, or metastatic setting with the exception for subjects who are clinically contraindicated for these chemotherapies.

[0153] (10) To be enrolled in the NSCLC expansion cohort, subjects must have: (a) Locally advanced or metastatic (stage IIIB, stage IV, or recurrent) NSCLC with measurable lesions per RECIST version 1.1. (b) PD during or following at least 1 prior treatment. Subjects should have received a prior platinum-containing, 2-drug regimen for locally advanced, unresectable/inoperable or metastatic NSCLC had or disease recurrence within 6 months of treatment with a platinum-based adjuvant/neoadjuvant regimen or combined modality (e.g., chemoradiation) regimen with curative intent. (c) Subjects with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic alternations should have PD on prior therapy for these aberrations. (d) Safely accessible tumor lesions (based on investigator's assessment) for serial pretreatment and posttreatment biopsies are required for subjects receiving Compound A monotherapy run-in treatment for 2 weeks followed by Compound A plus nivolumab combination treatment (approximately 10/30 response-evaluable subjects); adequate, newly obtained, core or excisional biopsy of a metastatic tumor lesion not previously irradiated is required. Mandatory biopsies will be taken before Compound A monotherapy, after the 2 weeks of Compound A monotherapy, and after 6 weeks of Compound A plus nivolumab combination therapy. An optional biopsy may be taken at PD with additional consent from the subject.

[0154] (11) To be enrolled in the HNSCC expansion cohort, subjects must have: (a) Histologically confirmed recurrent or metastatic HNSCC (oral cavity, pharynx, larynx), stage III/IV, and not amenable to local therapy with curative intent (surgery or radiation therapy with or without

chemotherapy). Histologically confirmed recurrent or metastatic squamous cell carcinoma of unknown primary or nonsquamous histologies (e.g., mucosal melanoma) are not allowed. Histologically confirmed recurrent or metastatic carcinoma of the nasopharynx is allowed, but these subjects will not be included as response-evaluable subjects for efficacy analysis of HNSCC. (b) Measurable disease per RECIST version 1.1. (c) Tumor progression or recurrence within 6 months of the last dose of platinum-based therapy in the adjuvant (i.e., with radiation after surgery), primary (i.e., with radiation), recurrent, or metastatic setting. (d) Safely accessible tumor lesions (based on investigator's assessment) for serial pretreatment and posttreatment biopsies are required for subjects receiving Compound A monotherapy run-in treatment for 2 weeks followed by Compound A plus nivolumab combination treatment (approximately 10/30 response-evaluable subjects); adequate, newly obtained, core or excisional biopsy of a metastatic tumor lesion not previously irradiated is required. Mandatory biopsies will be taken before Compound A monotherapy, after the 2 weeks of Compound A monotherapy, and after 6 weeks of Compound A plus nivolumab combination therapy. An optional biopsy may be taken at PD with additional consent from the subject.

Exclusion criteria:

[0155] (1) Has active brain metastases or leptomeningeal metastases.

[0156] (2) Has active, known, or suspected autoimmune disease.

[0157] (3) Diagnosis of immunodeficiency or any condition requiring systemic treatment with corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of treatment.

[0158] (4) Has history of pneumonitis requiring treatment with steroids; history of idiopathic pulmonary fibrosis, drug-induced pneumonitis, organizing pneumonia, or evidence of active pneumonitis on screening chest computed tomography scan; history of radiation pneumonitis in the radiation field (fibrosis) is permitted.

[0159] (5) Has history of interstitial lung disease.

[0160] (6) Prior therapy with experimental antitumor vaccines; any T-cell co-stimulation agents or inhibitors of checkpoint pathways, such as anti-programmed cell death protein 1 (PD-1), anti-programmed cell death 1 ligand 1 (PD-L1), anti-programmed cell death 1 ligand 2 (PD-L2), anti-CD137, or anti-CTLA-4 antibody; or other agents specifically targeting T cells are prohibited. However, in each of the expansion cohorts, 6 response-evaluable subjects with prior exposure to anti-PD-1 or anti-PD-L1 agents will be allowed to enroll.

[0161] (7) Has any serious medical or psychiatric illness, including drug or alcohol abuse, that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.

[0162] (8) Has life threatening-illness unrelated to cancer.

[0163] (9) Is female subject who are lactating and breast-feeding or a positive serum pregnancy test during the Screening period or a positive urine pregnancy test on Day 1 before the first dose of study drug.

[0164] (10) Systemic anticancer treatment or radiotherapy less than 2 weeks before the first dose of study treatment (≤ 4 weeks for monoclonal antibodies with evidence of PD) or not recovered from acute toxic effects from prior chemotherapy and radiotherapy.

[0165] (11) Prior treatment with investigational agents ≤ 21 days or $\leq 5 \times$ their half-lives (whichever is shorter) before the first dose of study treatment. A minimum of 10 days should elapse from prior therapy to initiating protocol therapy.

[0166] (12) Major surgery within 14 days before the first dose of study drug and not recovered fully from any complications from surgery.

[0167] (13) Systemic infection requiring intravenous antibiotic therapy or other serious infection within 14 days before the first dose of study drug.

[0168] (14) Treatment with high-dose corticosteroids for anticancer purposes within 14 days before the first dose of Compound A; daily dose equivalent to 10 mg oral prednisone or less is permitted. Corticosteroids for topical use or in nasal spray or inhalers are allowed.

[0169] (15) Known human immunodeficiency virus (HIV) positive (testing not required).

[0170] (16) Known hepatitis B surface antigen-positive or known or suspected active hepatitis C infection (testing not required).

[0171] (17) Active secondary malignancy that requires treatment. Subjects with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection and are considered disease-free at the time of study entry.

[0172] (18) Any clinically significant co-morbidities, such as uncontrolled pulmonary disease, known impaired cardiac function or clinically significant cardiac disease (specified below), active central nervous system disease, active infection, or any other condition that could compromise the subject's participation in the study. Subjects with any of the following cardiovascular conditions are

excluded: (a) Acute myocardial infarction within 6 months before starting study drug. (b) Current or history of New York Heart Association Class III or IV heart failure. (c) Evidence of current uncontrolled cardiovascular conditions including cardiac arrhythmias, angina, pulmonary hypertension, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities. (d) Friderichia corrected QT interval (QTcF) >450 milliseconds (msec) (men) or >475 msec (women) on a 12-lead electrocardiogram (ECG) during the Screening period. (e) Abnormalities on 12-lead ECG including, but not limited to, changes in rhythm and intervals that in the opinion of the investigator are considered to be clinically significant.

[0173] (19) Known gastrointestinal (GI) disease or GI procedure that could interfere with the oral absorption or tolerance of Compound A including difficulty swallowing tablets; diarrhea >Grade 1 despite supportive therapy.

[0174] (20) Use or consumption of any of the following substances: (a) Medications or supplements that are known to be inhibitors of P-glycoprotein (P-gp) and/or strong reversible inhibitors of within 5 times the inhibitor half-life (if a reasonable half-life estimate is known) or within 7 days (if a reasonable half-life estimate is unknown) before the first dose of study drug. The use of these agents is not permitted during the study. See Appendix G for a list of prohibited strong cytochrome P450 (CYP) 3A reversible inhibitors and/or P-gp inhibitors based on the US FDA draft DDI guidance. (b) Medications or supplements that are known to be strong CYP3A mechanism-based inhibitors or strong CYP3A inducers and/or P-gp inducers within 7 days, or within 5 times the inhibitor or inducer half-life (whichever is longer), before the first dose of study drug. The use of these agents is not permitted during the study. Grapefruit-containing food or beverages within 5 days before the first dose of study drug. (c) Grapefruit-containing food or beverages within 5 days before the first dose of study drug. Note that grapefruit-containing food and beverages are prohibited during the study.

[0175] (21) For dose expansion subjects who will have tumor biopsies collected: (a) ECOG performance status >1. (b) Activated partial thromboplastin time (aPTT) or plasma thromboplastin (PT) outside the normal range. (c) Platelet count <75,000/mcL. (d) Known bleeding diathesis or history of abnormal bleeding, or any other known coagulation abnormalities that would contraindicate the tumor biopsy procedure. (e) Ongoing therapy with any anticoagulant or antiplatelet agents (eg, aspirin, clopidogrel, coumadin, heparin, or warfarin) that cannot be held to permit tumor biopsy.

Main criteria for evaluation and analyses:

[0176] Primary endpoints: (1) MTD or RP2D (dose escalation). (2) ORR as assessed by the investigator per RECIST version 1.1 (dose expansion).

[0177] Secondary endpoints: (1) Percentage of subjects with adverse events (AEs), Grade 3 and Grade 4 AEs, serious AEs, and discontinuations for AEs, and clinical laboratory values and vital sign measurements outside the normal range that are of clinical significance. (2) Disease control rate. (3) DOR. (4) Rate of PD at 6 months. (5) PFS. (6) OS. (7) Summary statistics of Compound A maximum (peak) plasma concentration, first time to reach maximum (peak) plasma concentration, and area under the plasma concentration versus time curve over the dosing interval on Cycle 1, Days 1 and 15, by dose escalation cohort.

[0178] Statistical considerations: The MTD/MAD will be estimated by a standard 3+3 method using data collected in the dose escalation phase. AEs will be summarized by treatment group and overall. Categorical variables such as ORR, disease control rate, and rate of PD at 6 months will be tabulated by treatment group and overall. Time to event variables such as DOR, PFS, and OS will be analyzed using Kaplan-Meier survival curves, and Kaplan-Meier medians (if estimable) will be provided. PK parameters will be summarized as appropriate.

[0179] Sample size justification: During the dose escalation phase, dose escalation will be conducted according to a standard 3+3 dose escalation schema, and approximately 9 to 12 dose-limiting toxicity-evaluable subjects will be enrolled. The MTD/RP2D cohort will have at least 6 subjects. The sample sizes for each expansion cohort are estimated using a 1-sided exact binomial test at a significance level of $\alpha=0.1$ with a power of 80%. Each cohort uses a null hypothesis of response rate $\leq 20\%$, versus an alternative hypothesis of response rate $\geq 40\%$ for subjects who are naïve to anti-PD/PD-L1 and any other immune-directed antitumor therapies. Therefore, approximately 24 response-evaluable subjects for each cohort will be needed. In addition, 6 response-evaluable subjects with prior exposure to a PD-1 or PD-L1 inhibitor will be enrolled in each expansion cohort. In total, 30 response-evaluable subjects for each cohort and 90 response-evaluable subjects in total (~108 subjects based on a 15% drop-out rate) will be needed for all expansion cohorts.

Primary outcome measure:

[0180] (1) Part 1, MTD (baseline up to Day 28): MTD: highest dose level for which less than or equal to ($\leq$) 1 of 6 subjects in a dose cohort experience. Part 1, RP2D (baseline up to 6 months): the

RP2D of Compound A will be determined in Part 1 (dose escalation) on the basis of the safety, tolerability, preliminary pharmacokinetics (PK), and efficacy data observed in Cycle 1 and beyond.

[0181] (2) Part 2, ORR (baseline up to 6 months after the last dose of study treatment, approximately 18 months): ORR is defined as the percentage of subjects with complete response (CR), or partial response (PR) according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. CR is defined as complete disappearance of all target lesions and non-target disease, with the exception of nodal disease. All nodes, both target and non-target, must decrease to normal (short axis <10 mm). No new lesions. PR is defined as $\geq 30\%$ decrease under baseline of the sum of diameters of all target lesions. The short axis is used in the sum for target nodes, while the longest diameter is used in the sum for all other target lesions. No unequivocal progression of non-target disease. No new lesions.

Secondary outcome measures:

[0182] (1) Percentage of subjects experiencing 1 or more treatment-emergent adverse events (TEAEs) (baseline through 28 days after the last dose of study drug or to the start of subsequent alternative anticancer therapy, whichever occurs first (approximately up to 12 months)).

[0183] (2) Percentage of subjects with 1 or more grade 3 and grade 4 AEs (baseline through 28 days after the last dose of study drug or to the start of subsequent alternative anticancer therapy, whichever occurs first (approximately up to 12 months)).

[0184] (3) Percentage of subjects experiencing serious adverse events (SAES) (baseline through 28 days after the last dose of study drug or to the start of subsequent alternative anticancer therapy, whichever occurs first (approximately up to 12 months)).

[0185] (4) Percentage of subjects with TEAEs resulting in study drug discontinuation (baseline through 28 days after the last dose of study drug or to the start of subsequent alternative anticancer therapy, whichever occurs first (approximately up to 12 months)).

[0186] (5) Number of subjects with clinically significant laboratory values (baseline through 28 days after the last dose of study drug or to the start of subsequent alternative anticancer therapy, whichever occurs first (approximately up to 12 months)).

[0187] (6) Number of subjects with clinically significant vital sign measurements (baseline through 28 days after the last dose of study drug or to the start of subsequent alternative anticancer therapy, whichever occurs first (approximately up to 12 months)).

[0188] (7) Part 2: percentage of subjects with disease control (baseline up to 6 months after the last dose of study treatment (approximately 18 months)). Disease control rate: percentage of subjects with CR, PR or stable disease (SD) according to RECIST version 1.1. CR: complete disappearance of all target lesions and non-target disease, with exception of nodal disease.

[0189] (8) Part 2: Duration of Response (DOR) (from first dose until discontinuation of study drug due to disease progression, unacceptable toxicity, or death (approximately 18 months)). DOR is defined as the time from the date of first documentation of a response to the date of first documentation of PD according to RECIST version 1.1 criteria. PD is defined as $\geq 25\%$ increase from lowest value in: serum/urine M-component; difference between involved, uninvolved FLC levels; bone marrow plasma cell percent; development of new bone lesions or soft tissue plasmacytomas development or increase in the size of existing bone lesions or soft tissue plasmacytomas; hypercalcaemia development. Subjects without documentation of PD at the time of analysis will be censored at the date of their last response assessment that is SD or better.

[0190] (9) Part 2: percentage of subjects with progression of disease (PD) at Month 6. PD is defined as $\geq 25\%$ increase from lowest value in: serum/urine M-component; difference between involved, uninvolved FLC levels; bone marrow plasma cell percent; development of new bone lesions or soft tissue plasmacytomas development or increase in the size of existing bone lesions or soft tissue plasmacytomas; hypercalcaemia development.

[0191] (10) Part 2: progression free survival (PFS) (baseline up to 6 months after the last dose of study treatment (approximately 18 months)). Progression-free survival is defined as the time from the date of randomization to the date of first documentation of progressive disease or death due to any cause, whichever occurs first. PD is defined as $\geq 25\%$ increase from lowest value in: serum/urine M-component; difference between involved, uninvolved FLC levels; bone marrow plasma cell percent; development of new bone lesions or soft tissue plasmacytomas development or increase in the size of existing bone lesions or soft tissue plasmacytomas; hypercalcaemia development.

[0192] (11) Part 2: overall survival (OS) (baseline up to 6 months after the last dose of study treatment (approximately 18 months)). Overall survival is defined as the time from study entry to the time of death.

[0193] (12) Part 1: maximum observed plasma concentration (C_{max}) for Compound A (Cycle 1: Days 1 and 15: predose and at multiple time points (up to 8 hours)).

[0194] (13) Part 1: time to reach the C_{max} (T_{max}) for Compound A (Cycle 1: Days 1 and 15: predose and at multiple time points (up to 8 hours)).

[0195] (14) Part 1: area under the plasma concentration-time curve from time 0 to time tau (AUC_{tau})(Cycle 1: Days 1 and 15: predose and at multiple time points (up to 8 hours)).

Example 4: *In vivo* CT26 mouse syngeneic colon cancer model – re-challenge.

[0196] Purpose: To determine if the surviving mice from the previous CT-26 study can initiate an immune response against a re-challenge of the CT26 cell line.

[0197] The surviving mice were all previously treated with Compound A (60 mpk) plus anti-PD1 monoclonal antibody (Anti-PD-1) – in that previous study, female Balb/C mice (JAX) were inoculated with 0.2 x 10⁶ cells in left hind flank 7 days prior to randomization and treatment start. Compound (A) was administered orally (PO) on a once daily (QD) schedule for 14 days, while anti-PD-1 was administered at 10 mg/kg intraperitoneally (IP) for a total of 5 doses on days 0, 2, 6, 8, 11. Surviving combination therapy animals were followed for tumor progression. After 90 days, 11 of the 15 original animals remained tumor free. These animals were re-challenged with CT26 tumor cells on the opposite flank along with naïve cohort as a control. The take rate was 10 for 10 in the naïve group, while 0 out of 11 for the re-challenged survivors grew tumors. Compound A in combination with anti-PD-1 on the CT-26 syngeneic tumor model lead to vaccinal tumor memory.

[0198] 3 animals/group were removed at day 7, 14, and day 21 for FACS analysis. FACS analysis using pentamer was not able to identify CT26 specific T cells.

[0199] The CT26 colon carcinoma cell line is commonly used for syngeneic tumor model growth in the Balb/c mouse. CT26 colon carcinoma cells originate from *Mus musculus*, and subcutaneous inoculations develop to lethal tumors.

[0200] Animals: Balb/c mice from JAX (approximately 20 grams body weight) were used. They were group-housed and provided food and water ad libitum prior to the experiment. Mice were maintained on a 12-hour light and dark cycle and maintained in the vivarium for at least 7 days after receipt prior to investigations.

[0201] Drug preparation: No dosing in this re-challenge study.

[0202] Cell culture: CT26 cells (ATCC CRL-2638) were cultured in RPMI-1640, 10% FBS, +pen/strep. Media was changed every 2-3 days and cells were split at ~80% confluence. A maximum of 20 passages were allowed prior to re-initiating the culture from the original cell stock.

[0203] Animal preparation: Day -2 prior to tumor injection, the animals fur was shaved from the rump up to the middle of back and extended to the flank of each side. Caution was taken not to abrade the skin with the razor.

[0204] Tumor Injection (Day 0): the following procedure was followed: (a) aspirate media, wash cells with cold PBS, trypsinize to release, wash with PBS and collect cells; (b) spin, aspirate and resuspend in PBS, strain, spin again; (c) aspirate and resuspend in plain RPMI; (d) adjust cell concentration to $4 \times 10^6/\text{ml}$. Cells were kept cold. Matrigel stock was prepared. Cell stock and matrigel were mixed (1:1) to final cell concentration of $2 \times 10^6/\text{ml}$. The injection of 0.1 ml resulted in 0.2×10^6 cells/mouse. Animals were restrained and inoculated with 0.1ml of the cells plus matrigel subcutaneously in the flank. Bevel of needle was pointed up and rotated upon exit.

[0205] Tumor Growth (Day 7-21): Day 7 after inoculation, animals were sorted and randomized. Animals with abnormally small, large, or misshapen tumors were excluded prior to randomization. Prior to following randomization, animals were implanted subcutaneously with a micro tracker chip readable by the TMS system for identification. Tumors were measured by caliper (width x length) and body weight was recorded.

[0206] Study Design is shown in Table 4.

Table 4.

Group	Treatment	N
1	Naïve + CT26	10
2	CT26 survivors + CT26	11

[0207] Endpoints: tumor volume; body weight; FACS – Day 7, 14, 20: pentamer staining of blood, spleen, and bone marrow to try and identify CT26 specific T-cells.

[0208] Figure 6 exemplifies tumor volumes of re-challenged animals in CT-26 mouse syngeneic colon cancer model. Figure 7 exemplifies % mice with tumors for re-challenged animals in CT-26 mouse syngeneic colon cancer model.

Example 5: *In vivo* CT26 mouse syngeneic colon cancer model – immunosuppressive immune cells.

[0209] Compound A is a dual inhibitor of Spleen Tyrosine Kinase (SYK) and FLT3 that is being evaluated as a treatment for hematological malignancies in multiple clinical trials. SYK is a non-receptor cytoplasmic tyrosine kinase that is a common member of various signal transduction cascades in cells of the hematopoietic lineage including those involved in B-cell receptor (BCR) activation. With the recent success of immune checkpoint blockade agents in treating multiple types of cancer, increased attention has been paid in understanding the mechanism of the immune suppressive tumor microenvironment. Certain studies show that SYK inhibition results in loss of MDSCs and activation of T-cell response both in vitro and in vivo. This supports the combination of Compound A with anti-PD-1 therapy.

[0210] A study protocol was similar to the one for the treatment groups (1) Non-treated, (4) Compound A, (5) Anti-PD-1, and (8) Compound A + anti-PD-1 in Example 1.

[0211] Balb/C mice bearing CT-26 syngeneic tumors were treated with either Compound A 60 mg/kg, anti-PD-1 10mg/kg, or the combination for 14 days. Tumors were harvested, digested enzymatically, and assayed via flow cytometry to measure changes in the CD45+ tumor infiltrating lymphocytes. Compound A in combination with anti-PD-1 treatment resulted in a significant decrease in the B-cell and NK cell populations; a significant increase in the M1 macrophage population and decrease in the M2 macrophage population. Compound A single agent treatment significantly decreased the Treg cell population. See Figure 8, Figure 9, Figure 10, and Figure 11 for further details (* $P \leq 0.05$, ** $P \leq 0.01$, *** $P \leq 0.001$ One-Way ANOVA with Dunnett's multiple comparisons test, with a single pooled variance.).

[0212] Compound A + anti-PD-1 treatment significantly affected the immunosuppressive immune cells in the CT-26 model.

[0213] Flow cytometry to identify and enumerate different cell types in spleen and tumor: Spleens and tumors were removed and dissociated into single cell suspensions using the gentle MACS dissociator (Miltenyl Biotec). Spleens were processed in autoMACS buffer with 0.5% BSA and tumors in RPMI 1640 media with enzymes A, D and R provided in the MACS tumor dissociation kit. After red blood cell removal (eBioscience lysis buffer), cells were washed and suspended at 20×10^6 viable cells/ml. Single cell suspension was distributed into 96 well U bottom plate in PBS for viability staining (Zombie Aqua, Biolegend). Cells were then washed, blocked in Fc block (Becton Dickson and Company) and subsequently stained in 100ul final volume FACS buffer (PBS

+ 1% BSA). Conjugated antibodies for CD3, CD4, CD8, CD45, B220, PD-1, CD11b, $\gamma\delta$ TCR, ROR γ t and FoxP3 were purchased from eBioscience; NKp46, CD49b, Ly6G, Ly6C were purchased from BD biosciences; F4/80 was purchased from Biolegend. After staining, cells were washed and fixed in either fixation buffer (eBioscience) for surface stains or fixation/permeabilization buffer (eBioscience) for additional intracellular staining (FoxP3, ROR γ t). Cells were acquired on a Canto II flow cytometer (BD) and analyzed using the FloJo software. The data was retrieved off the machine and analyzed with GraphPad Prism (Version 5.04; GraphPad Software, Inc., La Jolla, CA, USA). Each individual mouse value was entered for the parameters that were of interest. Then a one-way ANOVA with a post-dunnet's multiple comparison test comparing all groups versus vehicle was done to determine significance. Results are expressed as mean $\pm$ standard error mean (SEM). A probability level of $p < 0.05$ was considered significant.

Example 6: *In vivo* subcutaneous B16BL16 murine melanoma model.

[0214] C57BL6 mice bearing syngeneic B16BL6 melanoma tumors were treated with Compound A 60 mg/kg QD PO for 7 days, and tumors were then collected and processed for flow cytometry. The percentage of MDSCs in the tumor infiltrating lymphocytes decreased following treatment with Compound A.

[0215] Each mouse (Mus musculus, female C57BL/6 mice; average weight 18.1 g at inoculation and 19.3 g at dosing initiation; 7-8 weeks age at inoculation; acclimation period 6 days) was inoculated subcutaneously at the right lower flank with B16BL6 tumor cells (2×10^5) in 0.1 ml of PBS for tumor development. Tumor growth was monitored with vernier calipers and the mean tumor volume (MTV) was calculated using the formula ($0.5 \times [\text{length} \times \text{width}^2]$). When the MTV reached 100 mm³, animals were randomized into treatment groups and dosed according to study design; dosing was initiated on Day 0 of the study. Mice were dosed PO with Compound A.

[0216] The mice in Compound A (60 mg/kg QD) group and 5 untreated tumor bearing mice were terminated post 7 days dosing for FACS analysis.

[0217] Study objective: To evaluate changes in immune cell population in tumors obtained at necropsy. Treatment was performed according to the schedule shown in Table 5. Cells were isolated from tumors. NK and MDSC cells were analyzed by FACS using specific antibodies. Antibody information and panel setting are described in Tables 6 and 7, respectively.

Table 5.

Group	N	Treatment
Untreated	5	none
Compound A	5	Compound A, 60 mg/kg, QD x 7, p.o.

Table 6.

Antibody	Fluorochrome	Catalogue #	Vendor
CD45	FITC	103108	Biolegend
CD11b	PEcy7	101216	Biolegend
Gr-1	PE	108408	Biolegend
CD335	PE	137604	Biolegend

Table 7.

Panel-1	CD45 FITC	CD335 PE	
Panel-2	CD45 FITC	Gr-1 PE	CD11b PEcy7

[0218] The results of the study are shown in Table 8 below ($P < 0.05$ for Compound A group, MDSC (CD11b+Gr-1+)). The percentage of MDSCs in the tumor infiltrating lymphocytes decreased following treatment with Compound A. See Figure 12.

Table 9.

Group	Percentage of immune cells in CD45+leukocytes of tumor	
	MDSC (CD11b+Gr-1+) for each animal	NK (CD335+) for each animal
Untreated	15.71%	1.44%
	22.93%	1.45%
	24.09%	1.79%
	23.07%	2.13%
	22.06%	1.79%
Compound A	15.57%	3.33%
	11.98%	1.44%
	15.45%	1.56%
	10.96%	1.69%
	22.25%	2.61%

Example 7: *In vivo* HCC70 triple negative breast cancer xenograph model.

[0219] Nude female mice bearing HCC70 triple negative breast cancer xenografts were administered a single dose of Compound A at 60mg/kg, tumors were harvested 8 and 24hrs post-dose and stained for CD11b+ positive cells via RNA scope. A decrease in MDSCs could be seen following Compound A treatment.

[0220] Study details: Female nude mice (Taconic Biosciences). HCC70 cell line was used. Number of cells implanted (in millions) – 5. Passage number – 9. Media – RPMI 1640. Matrigel support: no; estrogen: no. Implant route: SC. Implant site: flank (cell suspension). Drug: Compound A (PO, 60 mg/kg). Vehicle: 0.5 % methylcellulose. N=9 (n=3 for each treatment): Vehicle, Compound A 8hrs, and Compound A 24hr.

[0221] Methods: RNAscope ISH of CD11b (Green) and CD79a (Red) carried out by ACD. Images: Scanscope XT. Analysis: Definiens Tissue Studio; first analyzed as marker area/number of nuclei as in dual IHC; second analyzed CD11b only (real Area spot/number of nuclei) as in ISH. Data plots: Spotfire.

[0222] CD 11b and CD79a staining mostly in stromal regions. CD79a in red stained weak and may need further optimization. Two analysis methods yield similar result which shows CD11b in stromal regions decreased with Compound A treatment, but not reaching statistical significance due to rather large variations within each treatment group.

[0223] Figure 13 illustrates an effect of Compound A on MDSC (CD11b+) in HCC70 xenograph model.

Example 8: *In vivo* subcutaneous MH-22A murine liver cancer model in C3H/HeN mice.

[0224] The objective of the study is to evaluate the *in vivo* anti-tumor efficacy of Compound A in the treatment of the subcutaneous MH-22A murine liver cancer model in C3H/HeN mice as a single agent or in combination with anti-PD-1 therapy.

[0225] Test article – Compound A: it was formulated in 0.5% methyl cellulose (MC). Test Article – WX-mPD-1 (WuXi AppTech, Ltd., Shanghai China): it was formulated in WX-mPD1 buffer. Vehicle control article – methyl cellulose (Aladdin Biochemical Technology, Shanghai, China): it was formulated as 0.5% in water solution.

[0226] Test system – cell line: MH-22A (ECACC (96121721), Salisbury, England, UK); passage # (user stock) – P7; passage # (inoculated) – P11. Preparation media: DMEM + 2mM Glutamine + 10% FBS. Adherent or suspension: adherent. Initial viable cell conc. (cells/mL) in millions: 23. Volume of initial viable cell conc. used (mL): 22. Final conc. (cells/mL) in millions: 25. Matrigel: No. Volume of Final Cell Conc. (mL): 20.24. Cell number injected (millions): 5. Volume injected (mL): 0.2. Implant route: subcutaneous. Implant site: right flank.

[0227] Test system – animal: species -mouse. Strain: C3H/HeN. Source: Vital River. Beijing, China. Number of animals per group: 10. Total number of study animals: 40. Age: approximately 9 weeks at start of dosing. Sex: female. Weight: 21.6 grams at start of dosing. Acclimation period: at least 3 days.

[0228] Study design is shown in Table 10.

Table 10. Treatment Group	Number of Animals	Endpoints	Dose (mg/kg)	Injection Volume (mL/kg)	Conc. (mg/mL)	Route	Treatment Schedule	Treatment Days
Vehicle (0.5%MC)	10	%BWL	N/A	5	N/A	PO	QD x 21 days	0-21
Compound A	10	%TGI (a), %BWL (b), Δ AUC (p value) c, TGD	60	5	12	PO	QD x 21 days	0-21
WX-mPD-1	10	%TGI (a), %BWL (b), Δ AUC (p value) c, TGD	10	10	1	IP	BIW x 3 weeks	0, 3, 7, 10, 14, 17, 21
Compound A + WX-mPD-1	10	%TGI (a), %BWL (b), Δ AUC (p value) c, TGD	60 10	5 10	12 1	PO IP	QD x 21 days BIW x 3 weeks	0-21 0, 3, 7, 10, 14, 17, 21

Δ AUC = change in the area under the tumor volume-time curve; BIW = twice weekly; BWL = body weight loss; MC = methyl cellulose; IP = intraperitoneal(ly); kg = kilogram, N/A = not applicable; PO = per oral; QD = once daily; TGI = tumor growth inhibition.

Notes: a. TGI values were calculated on Day 9 of treatment. b. Mean maximum percent BWL. c.

Δ AUC = Statistical analysis was performed with a linear mixed effects regression model. A p value of < 0.05 was considered significant. d. TGD calculated when control tumors reach a volume of 1,000 mm³.

[0229] Approximately 8-week-old female C3H/HeN mice were inoculated subcutaneously with 5 x 10⁶ MH-22A liver tumor cells in the right flank. Tumor growth was monitored with vernier calipers and the mean tumor volume (MTV) was calculated using the formula (0.5 x [length x width²]). When the MTV reached approximately 103 mm³, animals were randomized into treatment groups (n = 10/group) and dosing was initiated on Day 0 of the study (Table 11). Tumor size and body weight were measured twice weekly and the study was terminated on day 94. By the termination, the Compound A single agent group had 2/10 animals with no tumor, the anti-PD-1 group had no complete or partial responders, while the combination treatment led to CRs in 6 animals (6/10) and SDs (a stable disease (SD) was defined as a decrease or a less than 25% increase in tumor mass from that at first treatment) in 2 animals (2/10). The other 2 animals (2/10) in the combination group were sacrificed due to the development of re-challenged tumor, but still with the primary tumors undetectable.

[0230] Table 11 shows study design and certain findings for the study.

Table 11.

Treatment Group	Dose (mg/kg)	Method of Administration /Frequency	Sex/ Number Per Group	Species/ Strain	Endpoints	Mean Tumor Volume (+/- SEM) mm ³	Findings
Vehicle (0.5%MC)	0.0	PO/ QD x 21 days	Female/10	Mouse (<i>Mus musculus</i>) C3H/HeN	TGI ^a	2034.2±975.2 ^e	N/A
					Maximum Mean %BWL ^b		0.3%, (Day 11)
Compound A	60	PO/ QD x 21 days	Female/10	Mouse (<i>Mus musculus</i>) C3H/HeN	TGI ^a	668.0±361.2 ^e	67.2%
					ΔAUC p-value ^c	35.4	p < 0.001
					Mean Maximum %BWL ^b		4.5%, (Day 18)
					TGD ^d		13.8
WX-mPD-1	10	IP/ BIW x 3 weeks	Female/10	Mouse (<i>Mus musculus</i>) C3H/HeN	TGI ^a	1176.7±583.4 ^e	42.2%
					ΔAUC p-value ^c	16.0	p = 0.045
					Mean Maximum %BWL ^b		0.0%
					TGD ^d		7.1
Compound A + WX-mPD-1	60; 10	PO/ QD x 21 days; IP/ BIW x 3 weeks	Female/10	Mouse (<i>Mus musculus</i>) C3H/HeN	TGI ^a	330.7±232.4 ^e	83.7%
					ΔAUC p-value ^c	57.1	p < 0.001
					Mean Maximum %BWL ^b		1.1%, (Day 18)
					TGD ^d		>88

ΔAUC = change in the area under the tumor volume-time curve; BIW = twice weekly; BWL = body weight loss; MC = methyl cellulose; IP = intraperitoneal(ly); kg = kilogram, N/A = not applicable; PO = per oral; QD = once daily; TGI = tumor growth inhibition.

Notes: a. TGI values were calculated on Day 9 of treatment. b. Mean maximum percent BWL, if mice gained weight this is reported as zero. c. ΔAUC = Statistical analysis was performed with a linear mixed effects regression model. A p value of < 0.05 was considered significant. d. TGD calculated when control tumors reach a volume of 1,000 mm³. e. Mean Tumor Volume on day of TGI calculation.

[0231] Tumor volume and body weight measurements: The mean maximum BWL was determined for each group using the mean body weight data from the treatment period (versus predose body weights), and the mean maximum percent body weight change was also calculated on the basis of predose body weights. Percent TGI was calculated on Day 9. Inhibition of tumor growth was determined by calculating the percent TGI using the following equation: Percent TGI = (MTV of the control group - MTV of a treated group) $\div$ MTV of the control group $\times$ 100.

[0232] Antitumor activity was determined by statistical comparisons of tumor growth between treatment groups and vehicle, conducted using a linear mixed effects regression analysis on the Δ AUC. In addition, antitumor efficacy was evaluated by TGD, which was calculated as the difference in the median time (Days) between the treated and the vehicle control group to attain the evaluation size of 1000 mm³.

[0233] Statistical Analysis – delta AUC: The differences in the tumor growth trends over time between the vehicle control and treatment groups were assessed using linear mixed effects regression models. These models take into account that each animal was measured at multiple time points. A model was fit for the comparison, and the areas under the tumor volume-time curve (AUCs) for control and treatment groups were calculated using the values predicted from the model. A statistically significant p value suggests that the trends over time for the 2 groups (vehicle and treatment) were different. A p value < 0.05 was considered statistically significant. Three animals in Vehicle control group and one animal in WX-mPD-1 group were excluded from statistical analysis due to the reasons specified below.

[0234] Modification to study design: All treatments were stopped at day 21 and the post-treatment observation was continued till the study termination on day 94. During the observation period, animals with tumor volume exceeding 2,000 mm³ were sacrificed, and no additional animal death occurred with any other causes. The accumulative numbers of animal loss in each group at different time-points were: (1) Vehicle: 3/10 at day 7, 7/10 at day 9, 8/10 at day 11, 9/10 at day 14 and 10/10 at day 21; (2) Compound A single agent: 2/10 at day 14, 3/10 at day 21, 4/10 at day 29, 5/10 at day 39, 6/10 at day 53, 7/10 at day 64, 8/10 at day 73 till the termination of study; (3) WX-mPD-1 single agent: 1/10 at day 7, 2/10 at day 9, 4/10 at day 11, 7/10 at day 14, 9/10 at day 23 and 10/10 at day 73; (4) Compound A and WX-mPD-1 combination: 1/10 at day 70 and 2/10 at day 84 till the end.

[0235] The end-point of TGI calculation and statistical analysis is day 9. All animals, which were already sacrificed by the end-point, were excluded from the TGI calculation and statistical analysis.

[0236] Figure 14-Figure 17 show the individual tumor growth of each animal in each treatment group for the duration of the study. Figure 18 shows average tumor volume over time in female C3H/HeN mice bearing MH-22A syngeneic model dosed with vehicle, Compound A, anti-PD-1, or Compound-A plus anti-PD-1 combination. Compound A as a single agent had 2/10 animals with no tumor at the end of study. In comparison, combination treatment resulted in durable anti-tumor activity, with 6/10 tumors having complete response on Day 51.

[0237] Compound A treatment at 60 mg/kg PO on a QD schedule combined with WX-mPD-1 at 10 mg/kg IP on a BIW schedule inhibited tumor growth (TGI = 83.7%) and demonstrated a statistically significant increase in antitumor activity when compared to vehicle treatment ($\Delta\text{AUC} = 57.1$, $p < 0.001$) in a MH-22A model of murine liver cancer. Compound A as a single agent dosed at 60 mg/kg PO, on a QD schedule resulted in a TGI = 67.2%, ($\Delta\text{AUC} = 35.4$, $p < 0.001$). Treatment with WX-mPD-1 resulted in $\Delta\text{AUC} = 16.0$, $p = 0.045$, with a TGI of 42.2%.

[0238] Combination treatment (Compound A and WX-mPD-1) resulted in therapeutic advantage over single-agent therapy in the MH-22A model of murine liver cancer, with durable inhibition of tumor growth out to Day 94 of the study. The combination treatment resulted in a tumor growth delay greater than 88 days, compared to 13.8 days in the Compound A single agent treatment, and 7.1 days in the anti-PD-1 treated group.

[0239] Compound A as a single agent had 2/10 animals with no tumor at the end of study. In comparison, the combination treatment resulted in durable anti-tumor activity, with 6/10 tumors having a complete response on Day 51. By the termination of the study, the anti-PD-1 group had no complete or partial responders, while the combination treatment led to CRs in 6 animals (6/10) and SDs in 2 animals (2/10). The other 2 animals (2/10) in the combination group were sacrificed due to the development of re-challenged tumor, but still with the primary tumors undetectable.

[0240] The mean maximum percent body weight loss was 4.5% in Compound A single agent group on Day 18 of the study. No deaths occurred in any groups during the treatment period of the study (except those which were sacrificed due to tumor development).

Example 9: *In vivo* MH-22A liver tumor syngeneic model in C3H/HeN mice – re-challenge.

[0241] Complete responders from the combination treatment from prior study were re-challenged with MH-22A tumor cells on the opposite flank with a naïve cohort as a control. 4/6 mice from the

pre-treated combination group maintained an inhibitory tumor growth response with no tumor formation, suggesting an anti-tumor vaccinal memory.

[0242] The objective of the study is to evaluate the tumor re-challenge of MH-22A liver tumor syngeneic model in the complete responders of female C3H mice which were treated by Compound A and WX-mPD-1 combination, and survived from the previous study (see Example 8).

[0243] Material and methods: no test and control articles.

[0244] Test System – cell line: Tumor cell line: MH-22A. Source: ECACC (96121721), Salisbury, England, UK. Passage # (user stock): P5. Passage # (inoculated): P8. Preparation media: DMEM + 2mM Glutamine + 10% FBS. Adherent or suspension: adherent. Initial viable cell conc. (cells/mL) in millions: 8.76. Volume of initial viable cell conc. used (mL): 20. Final conc. (cells/mL) in millions: 25. Matrigel: No. Volume of Final Cell Conc. (mL): 7.01. Cell number injected (millions): 5. Volume injected (mL): 0.2. Implant route: subcutaneous. Implant site: left flank.

[0245] Test system – animal: Species: Mouse. Strain: C3H. Source: Treated mice: Vital River, Beijing, China. Untreated mice: Sippr-BK, Shanghai, China. Number of animals per group: 6. Total number of study animals: 12. Age: treated mice - approximately 17 weeks at re-challenge; untreated mice - approximately 8 weeks at re-challenge. Sex: female. Weight: treated mice - 25.6 grams at re-challenge; untreated mice - 21.8 grams at re-challenge. Acclimation period: at least 3 days.

[0246] Endpoints: untreated mice (6 animals) - % BWL (body weight loss); treated mice from prior study (6 animals) - CR (a complete response was defined as a decrease in tumor mass to an undetectable size ($<50 \text{ mm}^3$) at the study termination at day 43, % BWL (mean maximum percent BWL).

[0247] Approximately 8-week-old female C3H untreated mice and approximately 17-week-old female C3H mice which treated by combination Compound A and anti-PD-1 and survived tumor-free from previous study were inoculated subcutaneously with 5×10^6 MH-22A tumor cells in the left flank. Tumor growth was monitored with vernier calipers and the mean tumor volume (MTV) was calculated using the formula ($0.5 \times [\text{length} \times \text{width}^2]$). Tumor size and body weight were measured twice weekly and the study was terminated on day 43. By the termination, all the untreated mice were sacrificed due to tumor growth, while there were still 4 previously treated mice (4/6) survived with CRs.

[0248] Tumor volume and body weight measurements: The mean maximum BWL was determined for each group using the mean body weight data from the measurement period (versus inoculation

body weights), and the mean maximum percent body weight change was also calculated on the basis of inoculation body weights.

[0249] The tumor re-challenge was evaluated by the count of survivors with CR by the termination of study (Day 43). CR was defined as a decrease in tumor mass to an undetectable size ($< 50 \text{ mm}^3$).

[0250] During the observation period, animals with tumor volume exceeding $2,000 \text{ mm}^3$ were sacrificed, and no additional animal death occurred with other cause. The accumulative numbers of animal loss in each group at different time-points were: (1) untreated mice - 4/6 at day 12, and 6/6 at day 14; (2) treated mice - 1/6 at day 19, and 2/6 at day 33 till the termination of study.

[0251] The complete responders survived from previous study, which were treated by combination of Compound A and WX-mPD-1, showed continued antitumor activity in the post-treatment tumor re-challenge. 4 of 6 treated mice showed CR at the termination of study on day 43 after re-challenge, while the CR number of untreated group was zero.

[0252] Figure 19 shows average tumor volume over time for the untreated female C3H mice or the tumor-free survivors from previous study (which were treated with Compound A and anti-PD-1 combination in the previous study) after re-challenge with MH-22A syngeneic model. Figure 20 shows an individual tumor volume over time of tumor-free survivors from previous study (where mice were treated with Compound A and anti-PD-1 combination) after re-challenge with MH-22A syngeneic model.

[0253] Compound A as a single agent or in combination with anti-PD-1 antibody treatment reduced the population of immunosuppressive immune cells (e.g. T reg cells, MDSCs, M2 macrophages, and NK cells) in multiple syngeneic or xenograft models. Compound A administered daily, orally, in combination with anti-PD-1 therapy in the CT-26 model resulted in complete tumor regressions and the animals were tumor free for 90 days post-treatment. When these animals were rechallenged with CT-26 tumor cells, they failed to form tumors suggesting a memory T-cell effect was established from the initial treatment period. Similar combination efficacy was observed in the A20 and MH-22A models. Taken together, Compound A treatment in combination with anti-PD-1 resulted in complete tumor growth suppression, prolonged tumor free survival and potential immune memory against tumor cells supporting the rationale for examining the addition of Compound A to anti-PD-1 therapy in the clinic.

[0254] Example 10: Clinical solid tumor study design — a study of Compound A in combination with nivolumab in subjects with advanced solid tumors.

[0255] Recent studies have shown that myeloid-derived suppressor cells (MDSCs) use CD79-ITAM signaling that uses SYK as a signaling mediator. Additionally, Fms-like tyrosine kinase 3 (FLT3) and its ligand have been shown to induce MDSCs in vitro. LECHNER et al., J. Transl. Med. 9:90 (2011).

[0256] MDSC-mediated immune suppression has been reported in many solid tumors, including, but not limited to breast cancer, head and neck, and NSCLC. COTECHINI et al., Cancer. J., 21(4): 343-50 (2015). In addition, a role of B cells in tumor immunity has been studied, and the requirement of B cells for tumor growth and metastasis has been documented. DILILLO et al., J. Immunol., 184(7):4006-4016 (2010). SYK is known to be essential for development, growth, and maintenance of B cells.

[0257] SYK inhibition results in the loss of MDSCs and activation of T-cell response, both in vitro and in vivo. See, e.g., LUGER et al., PLoS One, 8(10):e76115 (2013). Although preclinical experiments in tumors in which SYK-mediated MDSC or B-cell immunosuppression are active show that Compound A did not inhibit or activate T cells directly, in certain embodiments, synergistic activity may be observed when a PD-1 receptor inhibitor that promotes T-cell function is administered in combination with a SYK inhibitor. The benefit of administering an anti-PD-1 agent with Compound A has been observed nonclinically, as in Example 1, and this effect may be indirectly attributed to the decrease in CD11b⁺ MDSC or B220⁺ B cells in the tumor-infiltrating immune cells of Compound A-treated tumors.

[0258] Accordingly, the addition of a SYK inhibitor, such as Compound A, to an anti-PD-1 agent may improve tumor regression via modulation of the tumor-infiltrating immune cells and other immune cells in the tumor microenvironment. The make-up of the tumor microenvironment, which differs among different tumor types, informs the choice of diseases to be evaluated in this study. Tumors in which there is MDSC or B-cell suppression are of particular interest: nonclinical assessment suggests that tumors such as TNBC, NSCLC, and HNSCC show MDSC-mediated tumor immunosuppression.

[0259] The study intends to clinically evaluate the combination effect of Compound A and nivolumab in 3 advanced solid tumor types (TNBC, NSCLC, and HNSCC). With the reference response rate of ~20% observed with nivolumab monotherapy in each of these indications, added benefit of this combination regimen will be assessed by whether a significantly improved overall response rate (ORR; target ORR of 40%) is observed, along with assessment of other efficacy measures such as duration of response (DOR) and survival benefit. While the majority of the

subjects in each of the cohorts (24/30 response-evaluable subjects) should be naïve to anti-PD-1, anti-PD-L1, and any other immune-directed antitumor therapies, a small subset of 6/30 response-evaluable subjects with prior exposure to an anti-PD-1 or anti-PD-L1 agent will be enrolled to observe any combination effect of Compound A plus nivolumab in this relapsed/refractory setting with regard to the PD-1/PD-L1 blockade. In addition, after determining a safe and tolerable combination dose for Compound A when co-administered with nivolumab during the initial dose escalation stage of the study, a 2-week, single-agent Compound A treatment period before combination therapy is planned in 10 response-evaluable subjects in each of the expansion cohorts. Correlative science studies are planned in pretreatment and post-treatment tumor biopsies and peripheral blood samples taken from these subjects with the intent of having more mechanistic understanding of the role of SYK in the tumor immunity and direct tumor effect, if any.

[0260] This is an open-label, multicenter, phase 1b, dose escalation study of Compound A in combination with nivolumab in subjects with advanced solid tumors. The purpose of this study is to evaluate the maximum tolerated dose (MTD) or recommended Part 2 dose (RP2D), safety and efficacy of Compound A in combination with nivolumab in subjects with advanced solid tumors.

[0261] The drug being tested is Compound A. This study will look at the determination of MTD/RP2D and efficacy measured by overall response rate (ORR) in subjects who take Compound A in combination with nivolumab. The study will include a dose escalation phase (Part 1) and a dose expansion phase (Part 2).

[0262] The study will include a dose escalation phase (Part 1) and a dose expansion phase (Part 2). In the dose escalation phase, the subject population will consist of all-comer subjects with advanced solid tumors for whom 1 or more prior lines of therapy have failed and who have no effective therapeutic options available based on investigator assessment. The dose expansion phase will include 3 cohorts: (1) subjects with metastatic triple-negative breast cancer (TNBC) who have had ≥ 1 prior line of chemotherapy; (2) subjects with locally advanced or metastatic non-small cell lung cancer (NSCLC) that has progressed on or after a prior platinum-based chemotherapy; and (3) subjects with locally advanced or metastatic head and neck squamous cell carcinoma (HNSCC) that has progressed or recurred within 6 months of the last platinum-based chemotherapy.

[0263] It is estimated that approximately 126 subjects will be enrolled in the study: approximately 9 to 12 subjects among the dose escalation cohorts evaluating weight-based dosing of nivolumab, 3 to 6 subjects in the possible nivolumab fixed-dose evaluation cohort, and approximately 36 subjects (30 evaluable subjects + 15% drop off) in each of the 3 dose expansion cohorts. Subjects will be

assigned to 1 of the 4 treatment groups: Part 1 Compound A + Nivolumab; Part 2 Metastatic TNBC; Part 2 Metastatic NSCLC; and Part 2 Metastatic HNSCC.

[0264] Once enrolled in the study, subjects will be administered Compound A orally once daily during each 28-day treatment cycle. Subjects receiving the combination therapy will also receive nivolumab once every 2 weeks intravenously (IV) over 60 minutes on Day 1 and Day 15 of each 28-day treatment cycle (for subjects who receive 2 weeks of Compound A monotherapy before starting combination treatment, the first nivolumab infusion will be administered on Cycle 1 Day 15). On days when both Compound A and nivolumab will be administered, the Compound A dose will be administered first followed by the nivolumab infusion (infusion to begin within 30 minutes after the Compound A dose). Subjects, including those who achieve a complete response, may receive study treatment until they experience disease progression (PD) or unacceptable toxicities.

[0265] While the MTD/maximally administered dose (MAD)/RP2D of Compound A are being determined, the starting dose of nivolumab will be 3 mg/kg IV. The starting dose of Compound A will be 60 mg QD. Dose escalation will follow a standard 3+3 escalation scheme, and dosing will increase to 100 mg QD, provided that the safety and tolerability of the 60 mg dose has been demonstrated. Intermediate dose levels between 60 and 100 mg (e.g., 80 mg) or dose levels below the starting dose of 60 mg (e.g., 40 mg) may be also evaluated if appropriate. Dose escalation will continue until the maximum tolerated dose (MTD) is reached, or until 100 mg QD of Compound A (the maximally administered dose, (MAD)) is determined to be safe and tolerable, or until a recommended phase 2 dose (RP2D), if different from the MTD or MAD, has been identified on the basis of the safety, tolerability, and preliminary pharmacokinetic (PK) and efficacy data (if available) observed in Cycle 1 and beyond. At least 6 subjects will be evaluated at the RP2D (the MTD, MAD, or a lower dose as determined) before making a decision to advance to further dose expansion.

[0266] After the RP2D of Compound A has been identified, on the basis of evaluation of the combination with a weight-based dose of nivolumab (3 mg/kg), this RP2D of Compound A may be evaluated in combination with a fixed dose of 240 mg IV nivolumab following discussion between the investigator and sponsor. For single-agent nivolumab, the fixed dose is expected to have equivalent exposure, safety and efficacy as the weight-based (3 mg/kg) dose. If the nivolumab fixed dose is evaluated, 3 subjects will be initially enrolled into the cohort. Following evaluation of the safety, efficacy, and any available PK data, along with discussions between the investigator and sponsor, 3 additional subjects may be enrolled into the cohort for a total of 3 to 6 subjects. Following

evaluation of this fixed-dose cohort (if it is run), the dose of nivolumab may be switched from the 3 mg/kg weight-based dose to a fixed dose of 240 mg for all subjects ongoing in the study at the time of the switch and those to be enrolled after the switch. This decision will be made on the basis of an assessment of the change in clinical practice in different regions and upon discussion and agreement between the investigators and sponsor. If the nivolumab fixed-dose evaluation cohort is not run, the dose of nivolumab for all subjects in the dose expansion phase will be 3 mg/kg, unless the direct conversion to a fixed dose of nivolumab is justified by other available data.

[0267] After the combination RP2D (the MTD, MAD, or a lower dose) is determined, expansion cohorts are planned in subjects with TNBC, NSCLC, and HNSCC. Thirty response-evaluable subjects will be enrolled in each expansion cohort, including approximately 10 subjects in each cohort who are able to provide evaluable serial biopsies. Additionally, each expansion cohort will include 24 response-evaluable subjects who are naïve to anti-PD-1/anti-PD-L1 therapy and 6 response-evaluable subjects who are relapsed/refractory to prior anti-PD-1/anti-PD-L1 therapy. Ten response-evaluable subjects in each expansion cohort will first receive single-agent treatment with Compound A for 2 weeks at the RP2D previously determined in combination with nivolumab. Following the 2-week, single-agent treatment, Compound A treatment will continue (at the same dose) in combination with nivolumab during Week 3 and beyond.

[0268] The subset of expansion subjects who will be treated with single-agent Compound A at its combination RP2D during Weeks 1 and 2 should have accessible tumors for core or excisional biopsy and provide permission for the biopsies to be taken. These subjects will undergo mandatory biopsies before single-agent Compound A treatment begins, at the end of the 2-week treatment window, and after 6 weeks of treatment with Compound A in combination with nivolumab; an optional biopsy will also be taken at the time of PD. The biopsies will be used for biomarker analysis evaluating the effect of Compound A on tumor cells and on immune/stromal cells supporting tumor tissue.

[0269] The remaining 20 response-evaluable subjects in each expansion cohort will receive Compound A at its RP2D in combination with nivolumab, starting from Week 1, Day 1.

[0270] During dose escalation, serial blood samples for assessment of Compound A plasma PK will be collected for 24 hours after Compound A dosing on Cycle 1 Days 1 and 15, the days on which both Compound A and nivolumab are administered. Although the risk of drug-drug interaction between Compound A and nivolumab is predicted to be low, Compound A plasma PK following combination administration in the dose escalation will be compared with historical plasma PK

following single-agent administration to confirm no clinically meaningful differences in Compound A PK between the single-agent and combination settings. For purposes of population PK analysis, sparse collection of PK samples will occur in the expansion cohorts during both the single-agent and combination administration periods.

[0271] All subjects in the expansion cohorts will be treated until either PD or occurrence of unacceptable toxicities, withdrawal due to other reasons, or the study is terminated by the sponsor. The objectives of these expansion cohorts are to evaluate efficacy of Compound A in combination with nivolumab as measured by overall response rate (ORR) and to determine the safety and tolerability of Compound A in combination with nivolumab.

[0272] Primary Objectives: (1) To determine the MTD/RP2D of Compound A when administered in combination with nivolumab (dose escalation). (2) To determine the efficacy of Compound A plus nivolumab as measured by ORR (dose expansion).

[0273] Secondary Objectives: (1) To determine the safety and tolerability of Compound A when administered in combination with nivolumab. (2) To evaluate other efficacy measures such as disease control rate (response plus stable disease), duration of response (DOR), rate of PD at 6 months, progression-free survival (PFS), and overall survival (OS). (3) To characterize the plasma PK of Compound A when administered in combination with nivolumab.

Subject population:

[0274] Dose escalation: Subjects aged 18 years or older with advanced solid tumors for whom 1 or more prior lines of therapy have failed and who have no effective therapeutic options available based on investigator assessment. Dose expansion: Subjects aged 18 years or older with: (1) metastatic TNBC with ≥ 1 prior line of chemotherapy; (2) locally advanced or metastatic NSCLC that has progressed on or after a prior platinum-based chemotherapy; or (3) locally advanced or metastatic HNSCC that has progressed or recurred within 6 months of the last platinum-based chemotherapy.

Number of subjects:

[0275] It is expected that approximately 120 subjects will be enrolled in the study: approximately 9 to 12 subjects in the dose escalation cohort and approximately 36 subjects in each of the 3 dose expansion cohorts.

Dose level(s):

[0276] Compound A: oral daily dosing with 3+3 dose escalation planned at 60 and 100 mg. The RP2D determined in combination with nivolumab during dose escalation will be used for the possible fixed-dose evaluation cohort and dose expansion cohorts. Nivolumab: 3 mg/kg IV dosing over 60 minutes every 2 weeks (Day 1 and Day 15 of each 28-day cycle). If the 240 mg fixed-dose cohort is evaluated and deemed safe and tolerable, the dosing regimen may switch to 240 mg, on the basis of change in clinical practice and discussion between the investigator and sponsor. For subjects participating in the 2-week monotherapy run-in with Compound A, the first dose will be on Cycle 1 Day 15.

Duration of treatment:

[0277] Treatment will continue until disease progression (PD), unacceptable toxicities, completion of the study, or withdrawal due to other reasons. The estimated treatment duration is 12 months.

Route of administration:

[0278] Compound A: oral. Nivolumab: IV.

Period of evaluation:

[0279] PFS follow-up of 6 months (for subjects who discontinue due to reasons other than PD) and OS follow-up of 12 months from the last dose of study drug are planned.

Criteria for inclusion:

[0280] (1) Is a male or female subjects aged 18 years or older.

[0281] (2) Has eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.

[0282] (3) Female subjects who: (a) are postmenopausal for at least 1 year before the screening visit, or (b) are surgically sterile, or (c) if childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent through 180 days after the last dose of study drug, or (d) agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subjects. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. Male subjects, even if surgically sterilized (i.e., status postvasectomy), who: (a) agree to practice effective barrier contraception during the entire study treatment period and through 180 days after the last dose of study drug, or (b) agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subjects. Periodic abstinence (e.g., calendar, ovulation,

symptothermal, postovulation methods for the female partner) and withdrawal are not acceptable methods of contraception.

[0283] (4) Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the subjects at any time without prejudice to future medical care.

[0284] (5) Suitable venous access for the study-required blood sampling, including PK and pharmacodynamic sampling.

[0285] (6) Clinical laboratory values as specified below within 28 days before the first dose of study drug: (a) Total bilirubin must be less than equal to ($\leq$) 1.5*the upper limit of normal (ULN). (b) Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) must be $\leq$ 2.5*ULN. (c) Creatinine clearance must be greater than equal to ($\geq$) 60 milliliter per minute (mL/minute) as estimated by the Cockcroft Gault equation or based on urine collection (12 or 24 hours). (d) Hemoglobin must be greater than equal to ($\geq$) 9 gram per deciliter (g/dL), absolute neutrophil count (ANC) must be $\geq$ 1500 per microliter (/mcL), and platelet count must be $\geq$ 75,000/mcL. Lipase must be $\leq$ 1.5*ULN and amylase $\leq$ 1.5*ULN with no clinical symptoms suggestive of pancreatitis and cholecystitis. Blood pressure $\leq$ Grade 1 (hypertensive subjects are permitted if their blood pressure is controlled to $\leq$ Grade 1 by hypotensive medications and glycosylated HbA1C $\leq$ 6.5%.

[0286] (7) Recovered (i.e., $\leq$ Grade 1 toxicity) from the reversible effects of prior anticancer therapy.

[0287] (8) To be enrolled in the dose escalation phase of the study, subjects must have a radiographically or clinically evaluable tumor, but measurable disease as defined by RECIST version 1.1 is not required for participation in this study. EISENHAUER et al., Eur. J. Cancer, 45(2):228-247 (2009).

[0288] (9) To be enrolled in the TNBC expansion cohort, subjects must have: (a) Histologically confirmed, metastatic TNBC with measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. (b) Triple-negative disease (estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (HER 2) negativity) confirmed on a histological biopsy of a metastatic tumor lesion (receptor conversion not allowed). (c) Safely accessible tumor lesions (based on investigator's assessment) for serial pretreatment and posttreatment biopsies are required for subjects receiving Compound A monotherapy run-in treatment for 2 weeks followed by Compound A plus nivolumab combination treatment (similar

approximately 10/30 response-evaluable subjects); adequate, newly obtained, core or excisional biopsy of a metastatic tumor lesion not previously irradiated is required. Mandatory biopsies will be taken before Compound A monotherapy, after the 2 weeks of Compound A monotherapy, and after 6 weeks of Compound A plus nivolumab combination therapy. An optional biopsy may be taken at PD with additional consent from the subject. (d) One, two, or three line(s) of chemotherapy for metastatic disease and with progression of disease on last treatment regimen. For the purposes of this study, neoadjuvant and/or adjuvant chemotherapy regimens do not count as a prior line of therapy. Prior treatment must include an anthracycline and/or a taxane in the neoadjuvant, adjuvant, or metastatic setting with the exception for subjects who are clinically contraindicated for these chemotherapies.

[0289] (10) To be enrolled in the NSCLC expansion cohort, subjects must have: (a) Locally advanced or metastatic (stage IIIB, stage IV, or recurrent) NSCLC with measurable lesions per RECIST version 1.1. (b) PD during or following at least 1 prior treatment. Subjects should have received a prior platinum-containing, 2-drug regimen for locally advanced, unresectable/inoperable or metastatic NSCLC had or disease recurrence within 6 months of treatment with a platinum-based adjuvant/neoadjuvant regimen or combined modality (e.g., chemoradiation) regimen with curative intent. (c) Subjects with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic alternations should have PD on prior United States Food and Drug Administration-approved therapy for these aberrations. (d) Safely accessible tumor lesions (based on investigator's assessment) for serial pretreatment and posttreatment biopsies are required for subjects receiving Compound A monotherapy run-in treatment for 2 weeks followed by Compound A plus nivolumab combination treatment (approximately 10/30 response-evaluable subjects); adequate, newly obtained, core or excisional biopsy of a metastatic tumor lesion not previously irradiated is required. Mandatory biopsies will be taken before Compound A monotherapy, after the 2 weeks of Compound A monotherapy, and after 6 weeks of Compound A plus nivolumab combination therapy. An optional biopsy may be taken at PD with additional consent from the subject.

[0290] (11) To be enrolled in the HNSCC expansion cohort, subjects must have: (a) Histologically confirmed recurrent or metastatic HNSCC (oral cavity, pharynx, larynx), stage III/IV, and not amenable to local therapy with curative intent (surgery or radiation therapy with or without chemotherapy). Histologically confirmed recurrent or metastatic squamous cell carcinoma of unknown primary or nonsquamous histologies (e.g., mucosal melanoma) are not allowed. Histologically confirmed recurrent or metastatic carcinoma of the nasopharynx is allowed, but these

subjects will not be included as response-evaluable subjects for efficacy analysis of HNSCC. (b) Measurable disease per RECIST version 1.1. (c) Tumor progression or recurrence within 6 months of the last dose of platinum-based therapy in the adjuvant (i.e., with radiation after surgery), primary (i.e., with radiation), recurrent, or metastatic setting. (d) Safely accessible tumor lesions (based on investigator's assessment) for serial pretreatment and posttreatment biopsies are required for subjects receiving Compound A monotherapy run-in treatment for 2 weeks followed by Compound A plus nivolumab combination treatment (approximately 10/30 response-evaluable subjects); adequate, newly obtained, core or excisional biopsy of a metastatic tumor lesion not previously irradiated is required. Mandatory biopsies will be taken before Compound A monotherapy, after the 2 weeks of Compound A monotherapy, and after 6 weeks of Compound A plus nivolumab combination therapy. An optional biopsy may be taken at PD with additional consent from the subject.

Exclusion criteria:

[0291] (1) Has active brain metastases or leptomeningeal metastases.

[0292] (2) Has active or suspected autoimmune disease or a history of known autoimmune disease, with the exception of: subjects with vitiligo, type I diabetes mellitus, resolved childhood asthma/atopy, residual hypothyroidism due to autoimmune condition requiring only hormone replacement, psoriasis not requiring systemic treatment or conditions not expected to recur in the absence of an external trigger.

[0293] (3) Any condition requiring systemic treatment with corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days before first dose of study drug. Corticosteroids for topical use or in nasal spray are allowed, as are inhaled steroids and adrenal replacement steroid doses >10 mg daily in the absence of active autoimmune disease.

[0294] (4) Has history of pneumonitis requiring treatment with steroids; history of idiopathic pulmonary fibrosis, drug-induced pneumonitis, organizing pneumonia, or evidence of active pneumonitis on screening chest computed tomography scan; history of radiation pneumonitis in the radiation field (fibrosis) is permitted.

[0295] (5) Has history of interstitial lung disease.

[0296] (6) Prior therapy with experimental antitumor vaccines; any T-cell co-stimulation agents or inhibitors of checkpoint pathways, such as anti-programmed cell death protein 1 (PD-1), anti-programmed cell death 1 ligand 1 (PD-L1), anti-programmed cell death 1 ligand 2 (PD-L2), anti-CD137, or anti-CTLA-4 antibody; or other agents specifically targeting T cells are prohibited.

However, in each of the expansion cohorts, 6 response-evaluable subjects with prior exposure to anti-PD-1 or anti-PD-L1 agents will be allowed to enroll.

[0297] (7) Has any serious medical or psychiatric illness, including drug or alcohol abuse, that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.

[0298] (8) Has life threatening-illness unrelated to cancer.

[0299] (9) Is female subject who are lactating and breast-feeding or a positive serum pregnancy test during the Screening period or a positive urine pregnancy test on Day 1 before the first dose of study drug.

[0300] (10) Systemic anticancer treatment (including investigational agents) or radiotherapy <2 weeks before the first dose of study treatment (= $\leq$ 4 weeks for antibody-based therapy including unconjugated antibody, antibody-drug conjugate, and bi-specific T-cell engager agents; = $\leq$ 8 weeks for cell-based therapy or antitumor vaccine) or have not recovered from acute toxic effects from prior chemotherapy and radiotherapy.

[0301] (11) Prior treatment with investigational agents = $\leq$ 21 days or = $\leq$ 5*their half-lives (whichever is shorter) before the first dose of study treatment. A minimum of 10 days should elapse from prior therapy to initiating protocol therapy.

[0302] (12) Major surgery within 14 days before the first dose of study drug and not recovered fully from any complications from surgery.

[0303] (13) Systemic infection requiring intravenous antibiotic therapy or other serious infection within 14 days before the first dose of study drug.

[0304] (14) Known human immunodeficiency virus (HIV) positive (testing not required).

[0305] (15) Known hepatitis B surface antigen-positive or known or suspected active hepatitis C infection (testing not required).

[0306] (16) Subjects with another malignancy within 2 years of study start. Subjects with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection and are considered disease-free at the time of study entry.

[0307] (17) Any clinically significant co-morbidities, such as uncontrolled pulmonary disease, known impaired cardiac function or clinically significant cardiac disease (specified below), active central nervous system disease, active infection, or any other condition that could compromise the

subject's participation in the study. Subjects with any of the following cardiovascular conditions are excluded: (a) Acute myocardial infarction within 6 months before starting study drug. (b) Current or history of New York Heart Association Class III or IV heart failure. (c) Evidence of current uncontrolled cardiovascular conditions including cardiac arrhythmias, angina, pulmonary hypertension, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities. (d) Friderichia corrected QT interval (QTcF) >450 milliseconds (msec) (men) or >475 msec (women) on a 12-lead electrocardiogram (ECG) during the Screening period. (e) Abnormalities on 12-lead ECG including, but not limited to, changes in rhythm and intervals that in the opinion of the investigator are considered to be clinically significant.

[0308] (18) Known gastrointestinal (GI) disease or GI procedure that could interfere with the oral absorption or tolerance of Compound A including difficulty swallowing tablets; diarrhea >Grade 1 despite supportive therapy.

[0309] (19) Use or consumption of any of the following substances: (a) Medications or supplements that are known to be inhibitors of P-glycoprotein (P-gp) and/or strong reversible inhibitors of within 5 times the inhibitor half-life (if a reasonable half-life estimate is known) or within 7 days (if a reasonable half-life estimate is unknown) before the first dose of study drug. In general the use of inhibitors of P-glycoprotein (P-gp) and/or strong reversible inhibitors of cytochrome P450 (CYP)3A, such as amiodarone, azithromycin, captopril, carvedilol, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, nefazodone, posaconazole, quercetin, quinidine, ranolazine, ticagrelor, verapamil, and voriconazole is not permitted during the study. The list of prohibited strong cytochrome P450 (CYP) 3A reversible inhibitors and/or P-gp inhibitors is not exhaustive and is based on the US FDA draft DDI guidance. (b) Medications or supplements that are known to be strong CYP3A mechanism-based inhibitors, such as clarithromycin, conivaptan, mibefradil, telithromycin, or strong CYP3A inducers and/or P-gp inducers, such as avasimibe, carbamazepine, phenobarbital, phenytoin, primidone, rifabutin, rifapentine, rifampin, St John's wort, within 7 days, or within 5 times the inhibitor or inducer half-life (whichever is longer), before the first dose of study drug. The use of these agents is not permitted during the study. The list of prohibited strong CYP3A inducers and/or P-gp inducers is not exhaustive and is based on the US FDA draft DDI guidance. Grapefruit-containing food or beverages within 5 days before the first dose of study drug. (c) Non-oncology vaccine therapies for prevention of infectious diseases (e.g., human papillomavirus [HPV] vaccine) within 4 weeks of study drug administration. The inactivated seasonal influenza vaccine can be given to subjects before treatment and while on therapy without

restriction. Influenza vaccines containing live virus or other clinically indicated vaccinations for infectious diseases (e.g., pneumovax, varicella) may be permitted but must be discussed with the sponsor's medical monitor and may require a washout period before and after administration of vaccine. (d) Grapefruit-containing food or beverages within 5 days before the first dose of study drug. Note that grapefruit-containing food and beverages are prohibited during the study.

[0310] (20) For dose expansion subjects who will have tumor biopsies collected: (a) ECOG performance status >1 . (b) Activated partial thromboplastin time (aPTT) or plasma thromboplastin (PT) outside the normal range. (c) Platelet count $<75,000/\text{mcL}$. (d) Known bleeding diathesis or history of abnormal bleeding, or any other known coagulation abnormalities that would contraindicate the tumor biopsy procedure. (e) Ongoing therapy with any anticoagulant or antiplatelet agents (eg, aspirin, clopidogrel, coumadin, heparin, or warfarin) that cannot be held to permit tumor biopsy.

Main criteria for evaluation and analyses:

[0311] Primary endpoints: (1) MTD or RP2D (dose escalation). (2) ORR as assessed by the investigator per RECIST version 1.1 (dose expansion).

[0312] Secondary endpoints: (1) Percentage of subjects with adverse events (AEs), Grade 3 and Grade 4 AEs, serious AEs, and discontinuations for AEs, and clinical laboratory values and vital sign measurements outside the normal range that are of clinical significance. (2) Disease control rate. (3) DOR. (4) Rate of PD at 6 months. (5) PFS. (6) OS. (7) Summary statistics of Compound A maximum (peak) plasma concentration, first time to reach maximum (peak) plasma concentration, and area under the plasma concentration versus time curve over the dosing interval on Cycle 1, Days 1 and 15, by dose escalation cohort.

[0313] Statistical considerations: The MTD/MAD (in combination with 3 mg/kg IV nivolumab) will be estimated by a standard 3+3 method using data collected in the dose escalation phase. AEs will be summarized by treatment group and overall. Categorical variables such as ORR, disease control rate, and rate of PD at 6 months will be tabulated by treatment group and overall. Time to event variables such as DOR, PFS, and OS will be analyzed using Kaplan-Meier survival curves, and Kaplan-Meier medians (if estimable) will be provided. PK parameters will be summarized as appropriate.

[0314] Sample size justification: During the dose escalation phase, dose escalation will be conducted according to a standard 3+3 dose escalation schema, and approximately 12 to 18 dose-

limiting toxicity-evaluable subjects will be enrolled (including 3 to 6 subjects in the possible nivolumab fixed-dose evaluation cohort). The MTD/RP2D cohort will have at least 6 subjects. The sample sizes for each expansion cohort are estimated using a 1-sided exact binomial test at a significance level of $\alpha=0.1$ with a power of 80%. Each cohort uses a null hypothesis of response rate $\leq 20\%$, versus an alternative hypothesis of response rate $\geq 40\%$ for subjects who are naïve to anti-PD/PD-L1 and any other immune-directed antitumor therapies. Therefore, approximately 24 response-evaluable subjects for each cohort will be needed. In addition, 6 response-evaluable subjects with prior exposure to a PD-1 or PD-L1 inhibitor will be enrolled in each expansion cohort. In total, 30 response-evaluable subjects for each cohort and 90 response-evaluable subjects in total (~108 subjects based on a 15% drop-out rate) will be needed for all expansion cohorts.

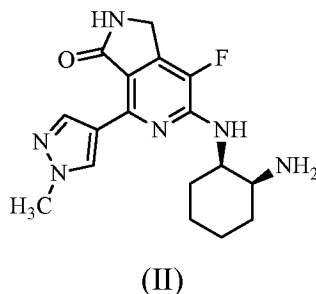
[0315] The embodiments described herein are intended to be merely exemplary, and those skilled in the art will recognize, or will be able to ascertain using no more than routine experimentation, numerous equivalents of specific compounds, materials, and procedures. All such equivalents are considered to be within the scope of the disclosure.

[0316] All of the patents, patent applications and publications referred to herein are incorporated herein in their entireties. Citation or identification of any reference in this application is not an admission that such reference is available as prior art to this application. The full scope of the disclosure is better understood with reference to the appended claims.

CLAIMS

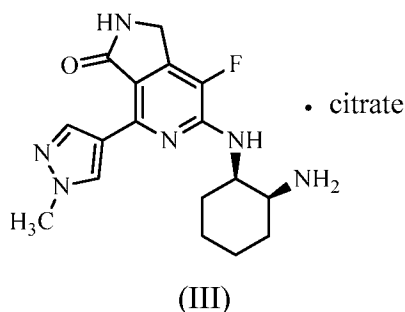
We claim:

1. A method of treating a cancer comprising administering to a subject having a cancer a therapeutically effective amount of a combination comprising:
an immunotherapy agent; and
a SYK inhibitor.
2. The method of claim 1, wherein the SYK inhibitor is a compound of Formula II:



or a pharmaceutically acceptable salt thereof.

3. The method of claim 1 or 2, wherein the SYK inhibitor is a compound of Formula III:



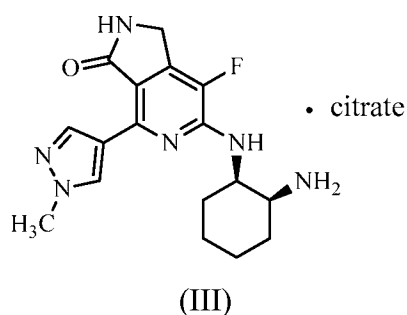
or a crystalline form thereof.

4. The method of any one of claims 1 to 3, wherein the immunotherapy agent is selected from a PD-1 inhibitor and a PD-L1 inhibitor.
5. The method of claim 4, wherein the immunotherapy agent is a PD-1 inhibitor.
6. The method of any one of claims 1 to 5, wherein the immunotherapy agent is selected from nivolumab and pembrolizumab.
7. The method of claim 6, wherein the immunotherapy agent is nivolumab.

8. The method of claim 6, wherein the immunotherapy agent is pembrolizumab.
9. The method of any one of claims 1 to 8, wherein the cancer is selected from breast cancer, lung cancer, head and neck cancer, melanoma, renal cancer, liver cancer, pancreatic cancer, colorectal cancer, ovarian cancer, gastric cancer, endometrial cancer, prostate cancer, brain and spine cancer, fallopian tube cancer, uterine cancer, bladder cancer, esophageal cancer, biliary tract cancer, urothelial cancer, soft tissue cancer, rectal cancer, thyroid cancer, bone cancer, salivary gland cancer, nasal cavity and paranasal sinus cancer, testicular cancer, adrenocortical cancer, thymic cancer, eye cancer, and gallbladder cancer.
10. The method of any one of claims 1 to 9, wherein the cancer is selected from breast cancer, lung cancer, head and neck cancer, melanoma, renal cancer, liver cancer, pancreatic cancer, colorectal cancer, ovarian cancer, gastric cancer, endometrial cancer, and prostate cancer.
11. The method of any of claims 1 to 10, wherein the cancer is selected from breast cancer, lung cancer, and head and neck cancer.
12. The method of any of claims 1 to 11, wherein the cancer is breast cancer.
13. The method of claim 12, wherein the breast cancer is triple negative breast cancer.
14. The method of any of claims 1 to 11, wherein the cancer is lung cancer.
15. The method of claim 14, wherein the cancer is non-small cell lung cancer.
16. The method of any of claims 1 to 11, wherein the cancer is head and neck cancer.
17. The method of claim 16, wherein the cancer is head and neck squamous cell carcinoma.
18. The method of any one of claims 1 to 17, wherein the SYK inhibitor is administered once daily.
19. The method of any one of claims 1 to 18, wherein the immunotherapy agent is administered once every two weeks on day 1 and day 15 of a 28-day cycle.
20. The method of any one of claims 1 to 18, wherein the PD-1 inhibitor or the PD-L1 inhibitor is administered once every three weeks.

21. The method any one of claims 1 to 19, wherein a dose of the SYK inhibitor is about 20 mg to about 150 mg per day.
22. The method of claim 21, wherein the dose of the SYK inhibitor is about 60 mg per day, and wherein the SYK inhibitor is administered once daily.
23. The method of claim 21, wherein the dose of the SYK inhibitor is about 80 mg per day, and wherein the SYK inhibitor is administered once daily.
24. The method of claim 21, wherein the dose of the SYK inhibitor is about 100 mg per day, and wherein the SYK inhibitor is administered once daily.
25. The method of any one of claims 1 to 24, wherein the immunotherapy agent is weight-based or fixed dose based.
26. The method of any one of claims 1 to 24, wherein the immunotherapy agent is administered intravenously.
27. The method of any one of claims 1 to 26, wherein the SYK inhibitor is administered orally.
28. The method of any one of claims 1 to 27, wherein the immunotherapy agent is administered intravenously and the SYK inhibitor is administered orally.
29. The method of any of claims 1 to 28, wherein the immunotherapy agent is administered as a liquid dosage form.
30. The method of any of claims 1 to 29, wherein the SYK inhibitor is administered as a solid dosage form.
31. The method of any one of claims 1 to 30, wherein the immunotherapy agent and the SYK inhibitor are administered simultaneously.
32. The method of any one of claims 1 to 30, wherein the immunotherapy agent and the SYK inhibitor are administered sequentially.
33. The method of claim 32, wherein the immunotherapy agent is administered prior to the SYK inhibitor.

34. The method of claim 32, wherein the SYK inhibitor is administered prior to the immunotherapy agent.
35. The method of any one of claims 1 to 34, wherein the combination further comprises one or more additional therapeutic agents.
36. A medical kit for treating a cancer comprising a therapeutically effective amount of a combination comprising:
an immunotherapy agent; and
a SYK inhibitor.
37. The medical kit of claim 36, wherein the SYK inhibitor is a compound of Formula III:



or a crystalline form thereof, and
wherein the immunotherapy agent is nivolumab.

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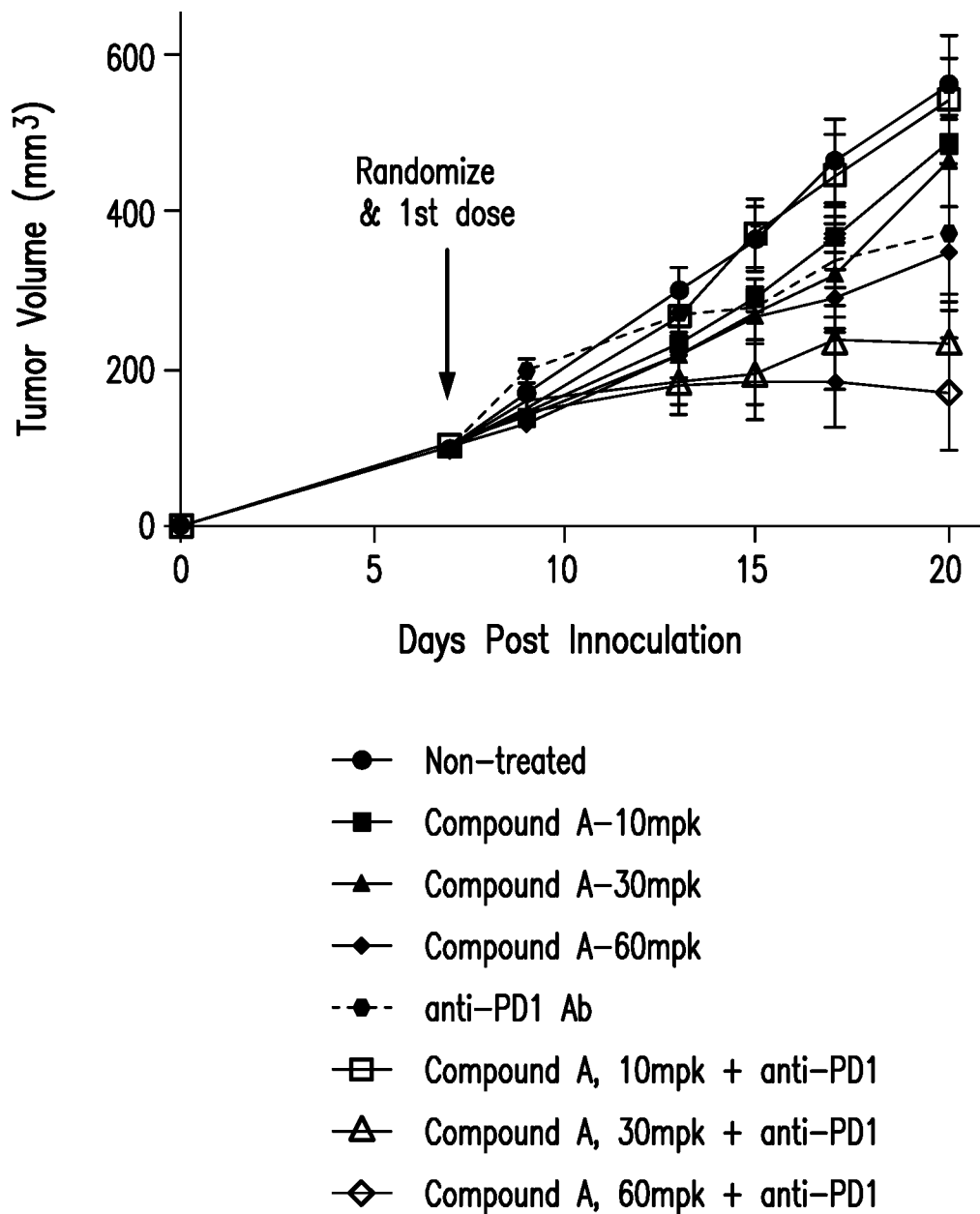
CT26_07 Tumor Growth Curve
(mean $\pm$ sem, n = 10)

FIG. 1

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CT26 _07 Survival Curve

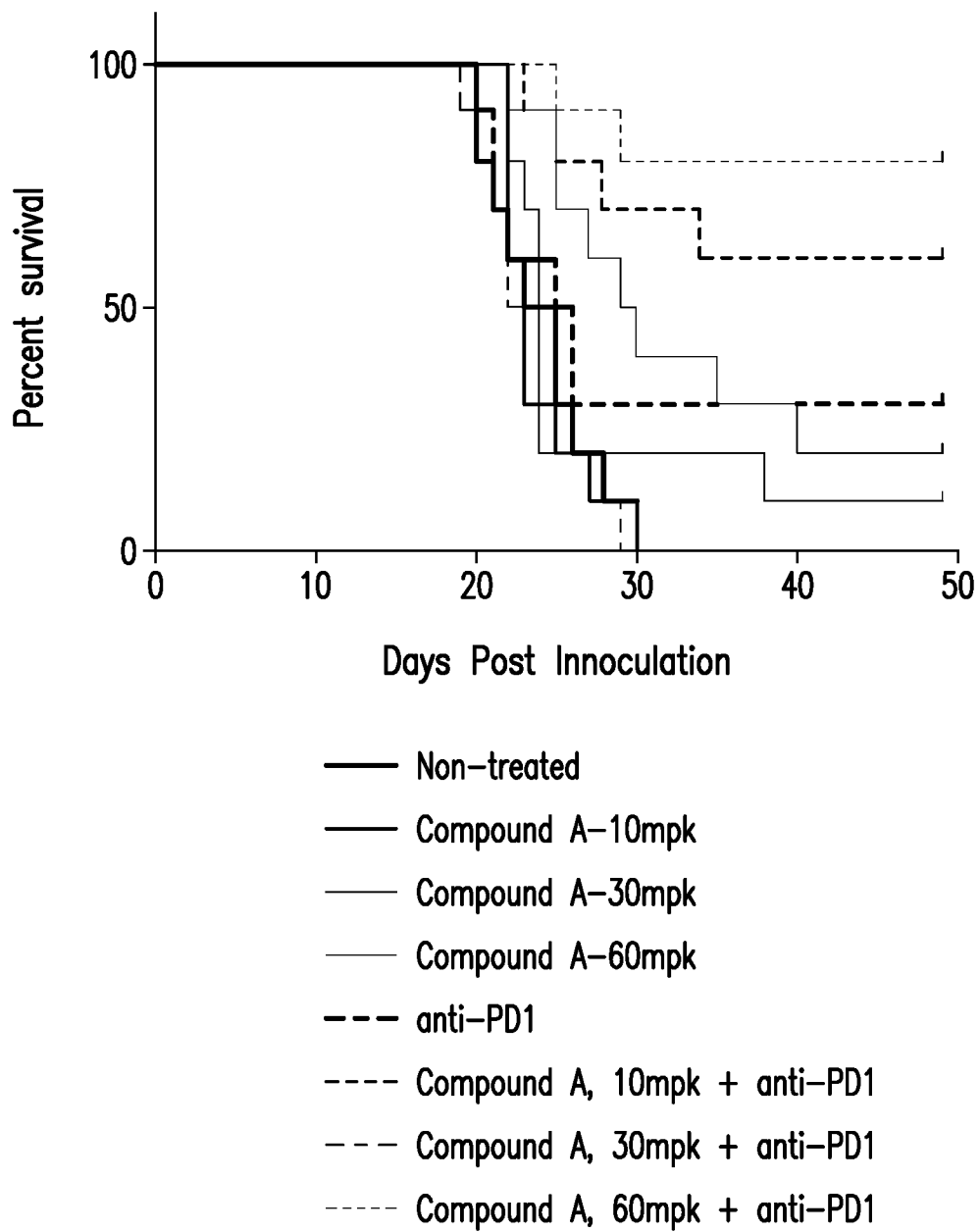


FIG. 2

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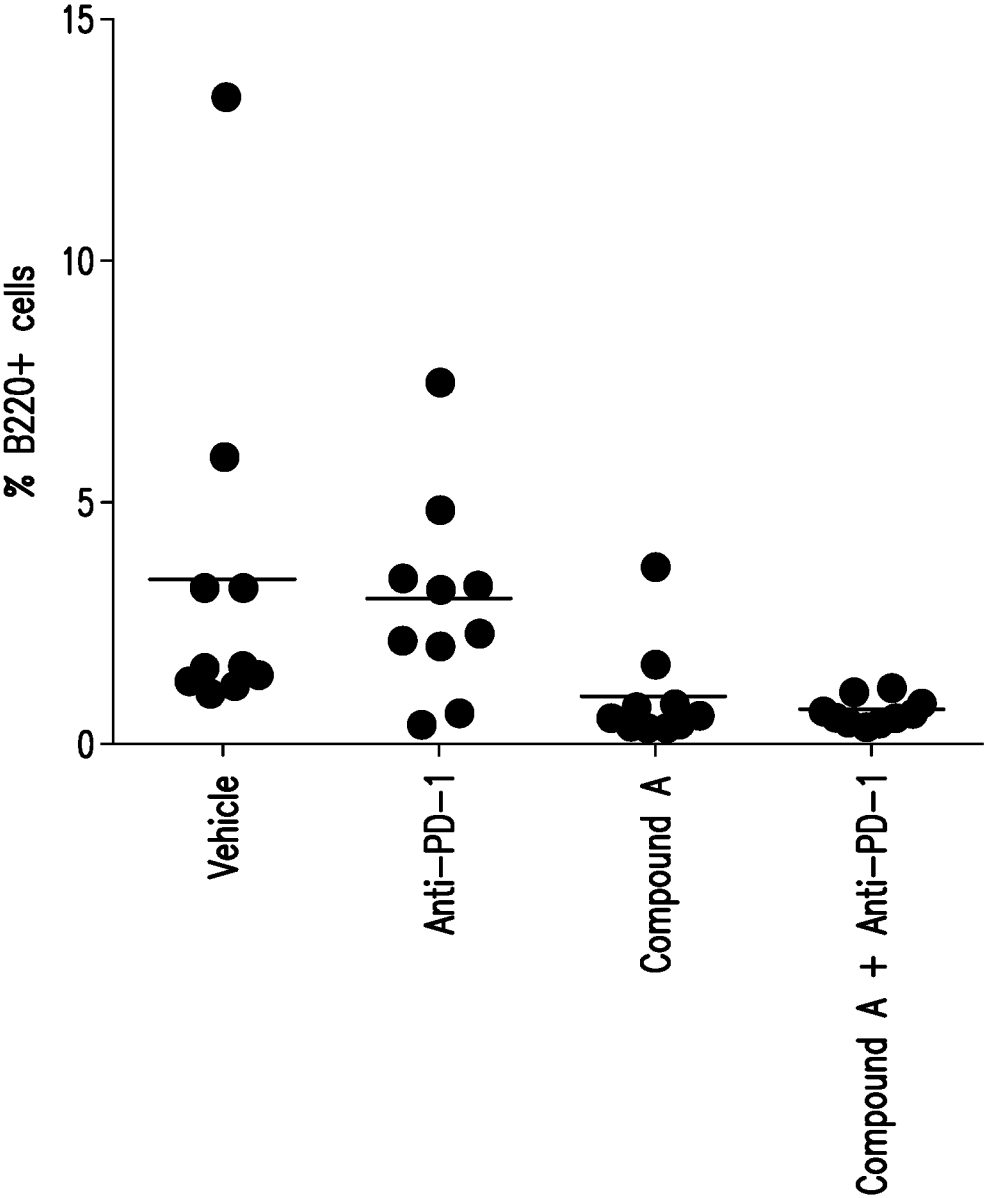


FIG. 3

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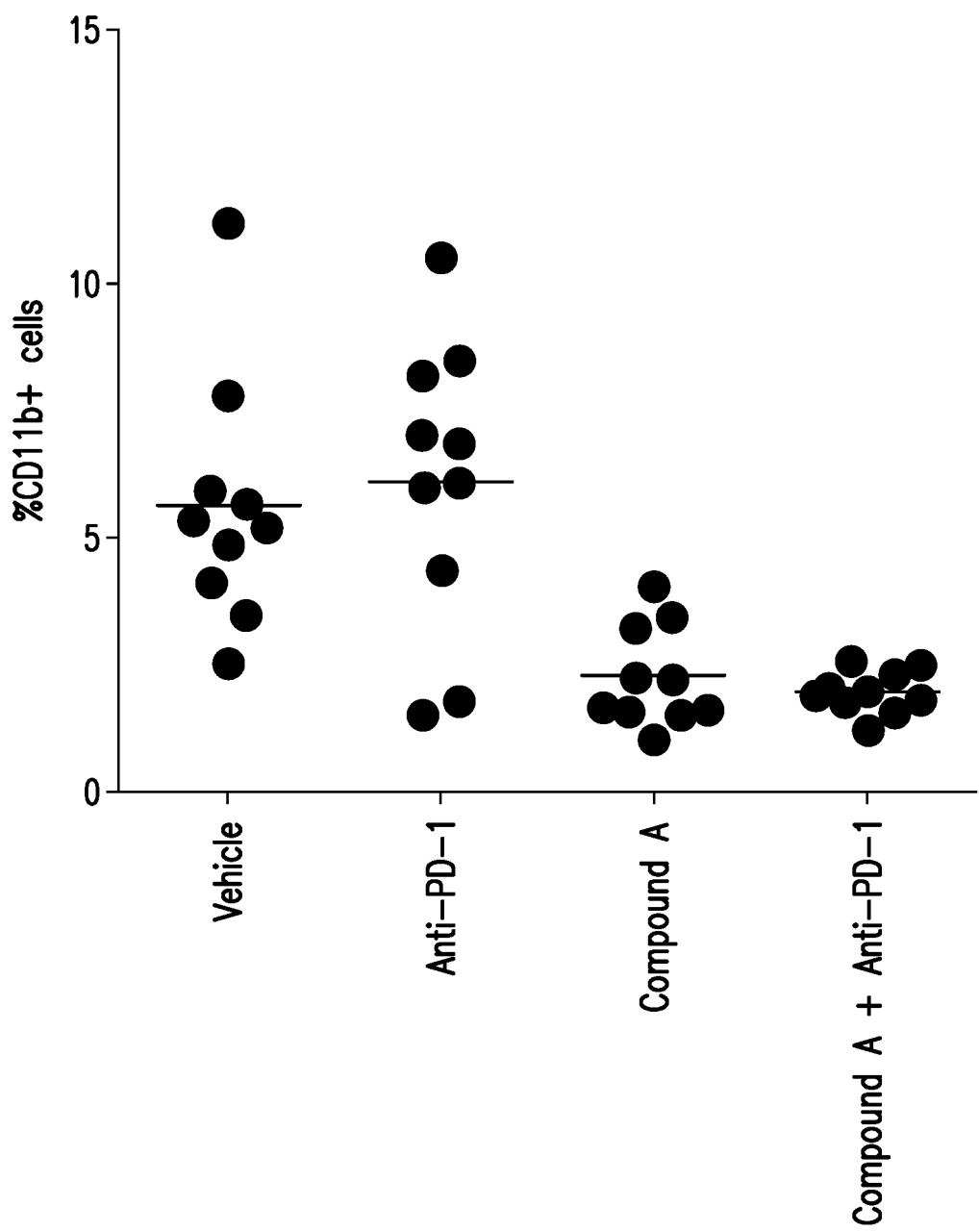


FIG. 4

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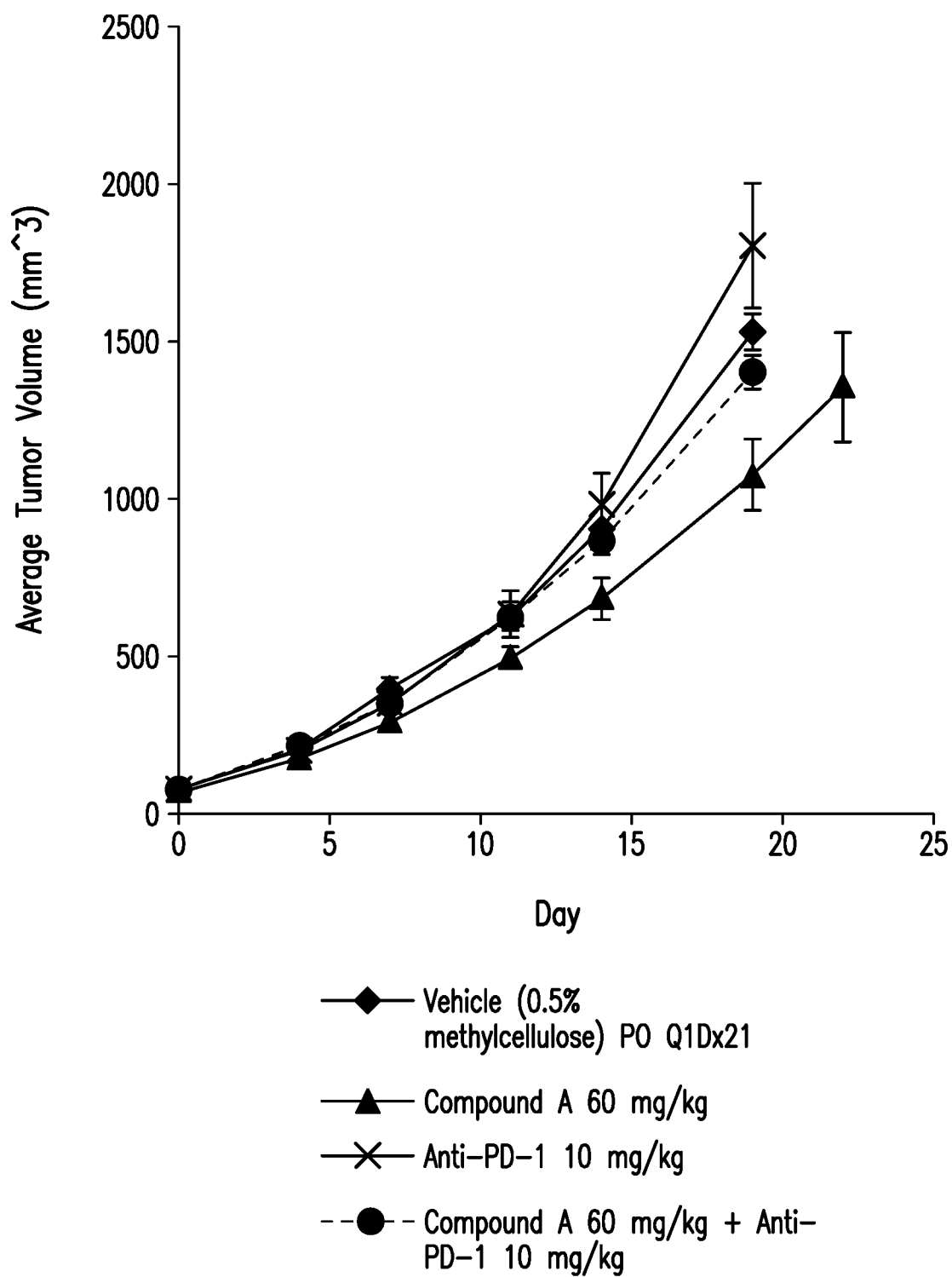


FIG. 5

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CT-26 Re-challenge

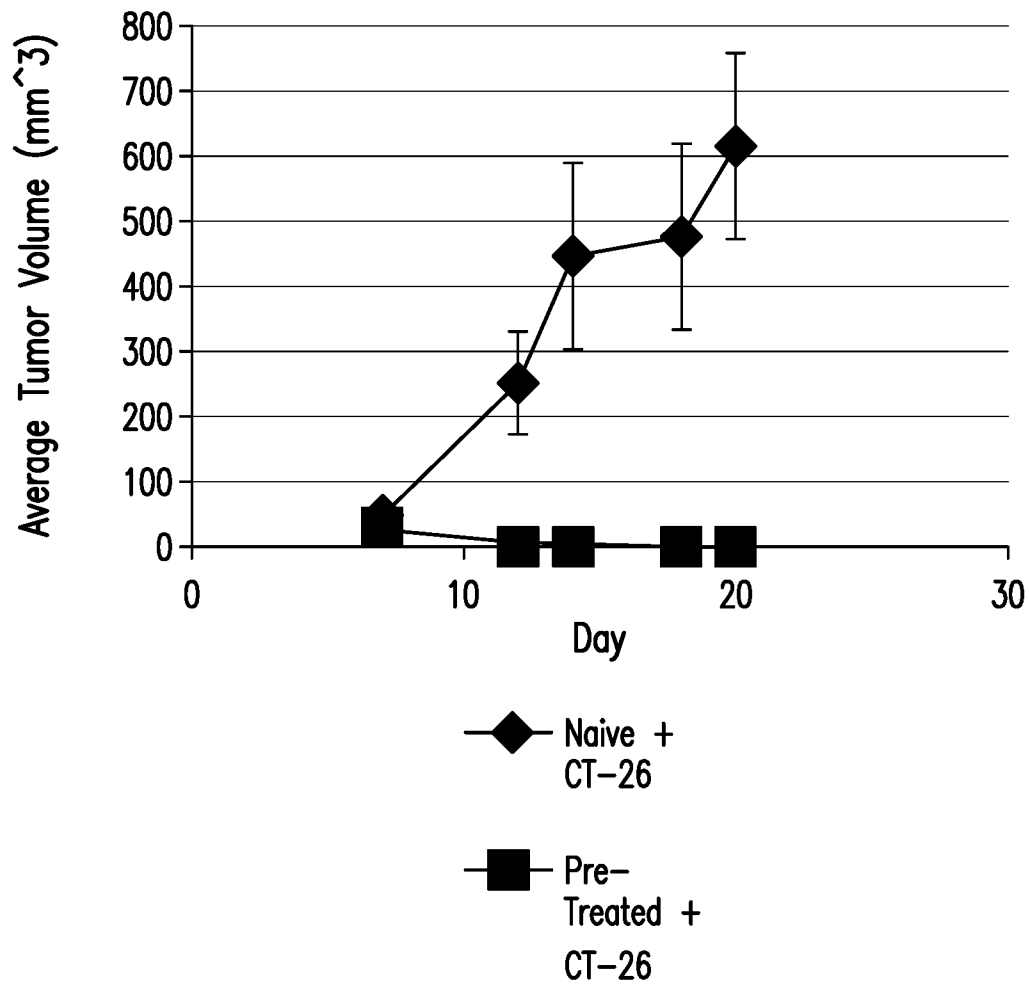
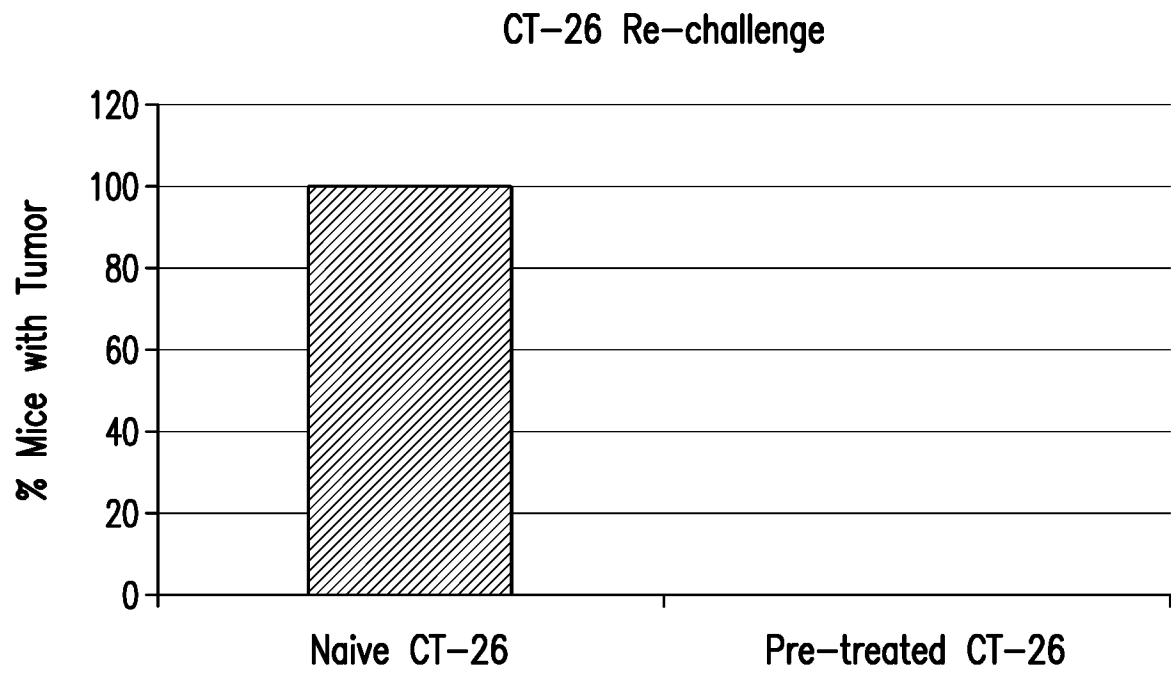


FIG. 6

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**FIG. 7**

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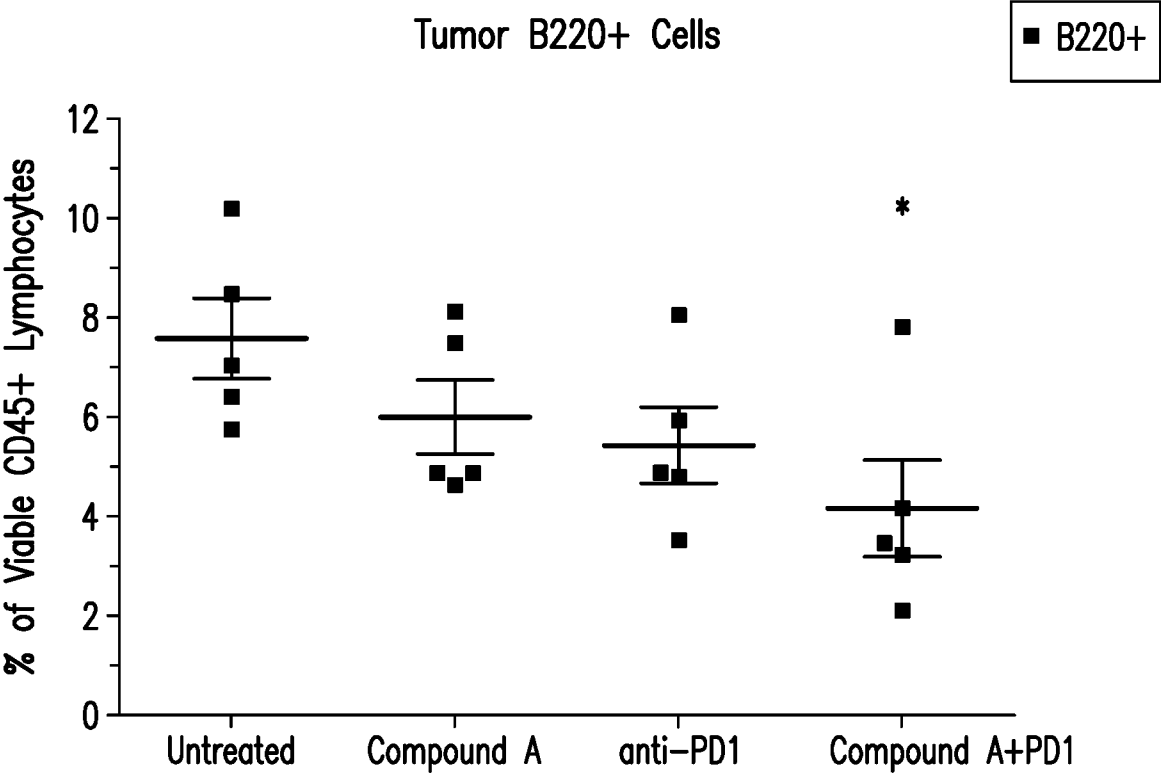


FIG. 8

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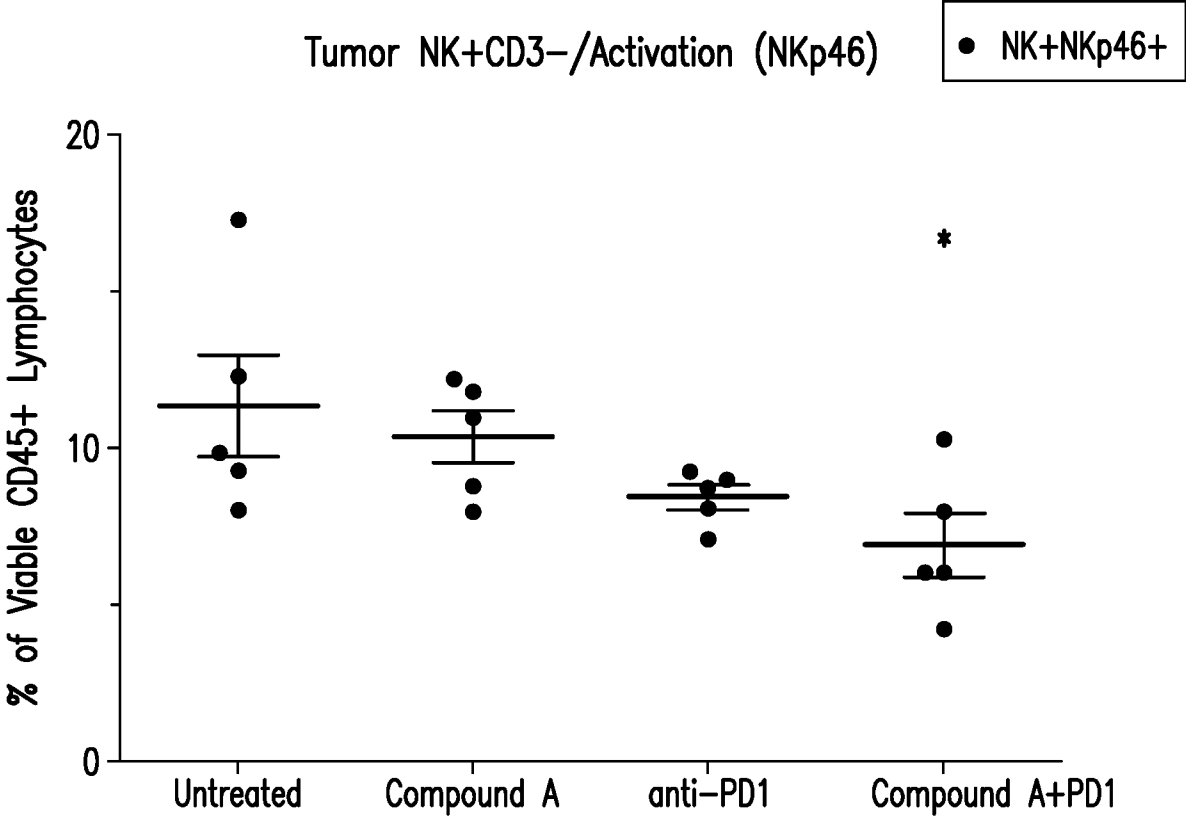


FIG. 9

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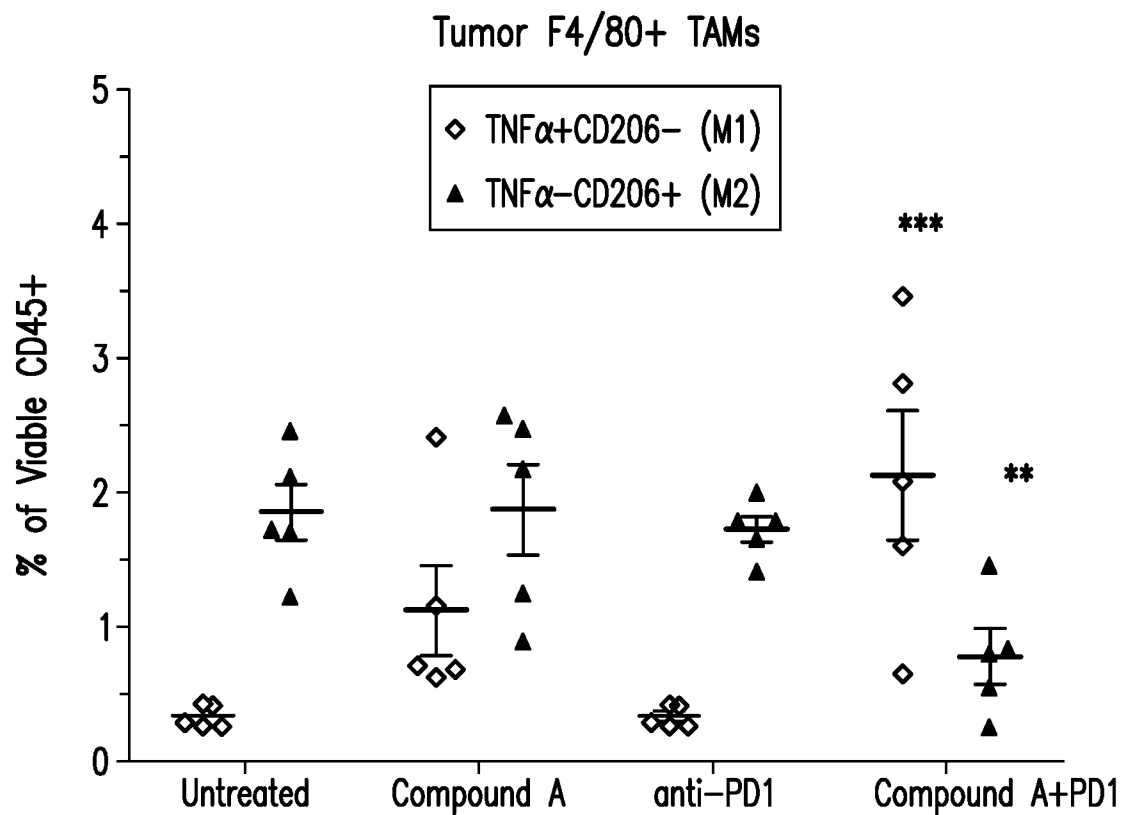


FIG. 10

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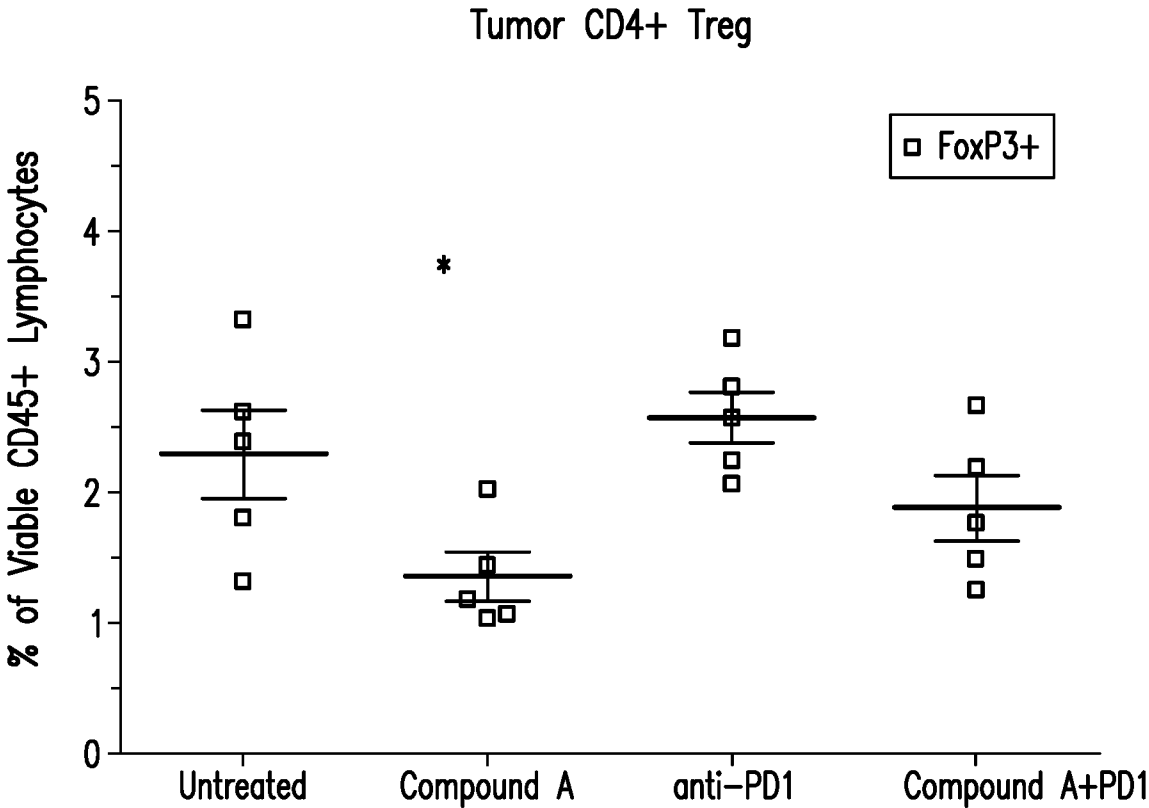


FIG. 11

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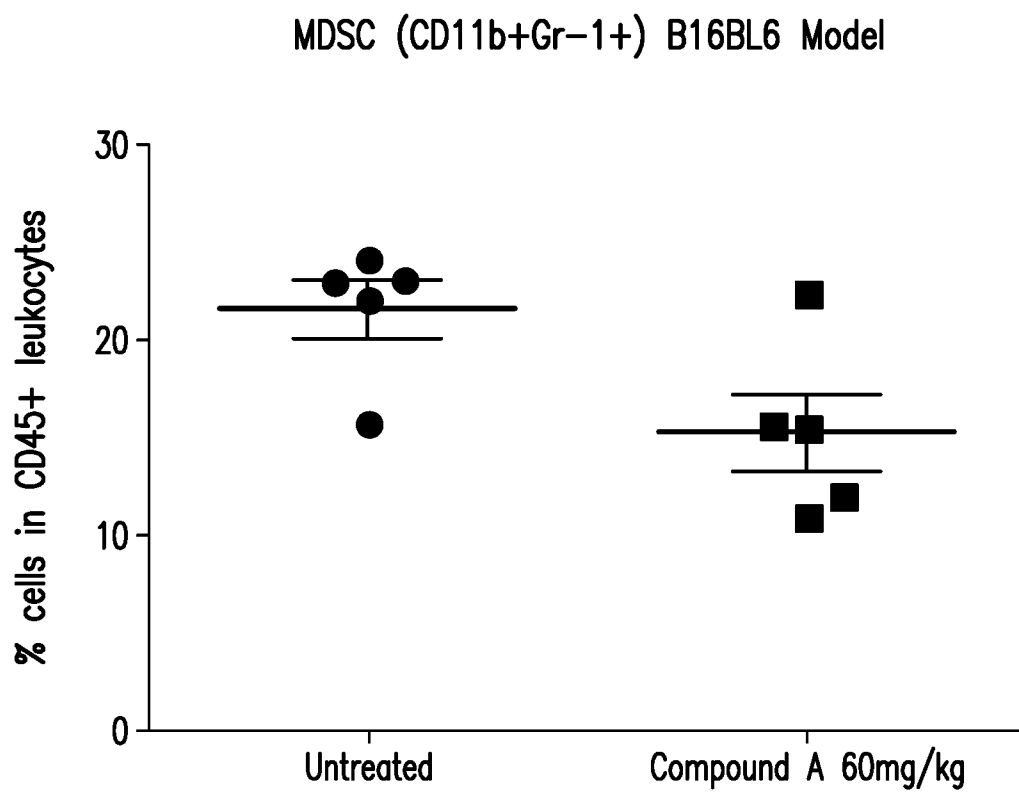


FIG. 12

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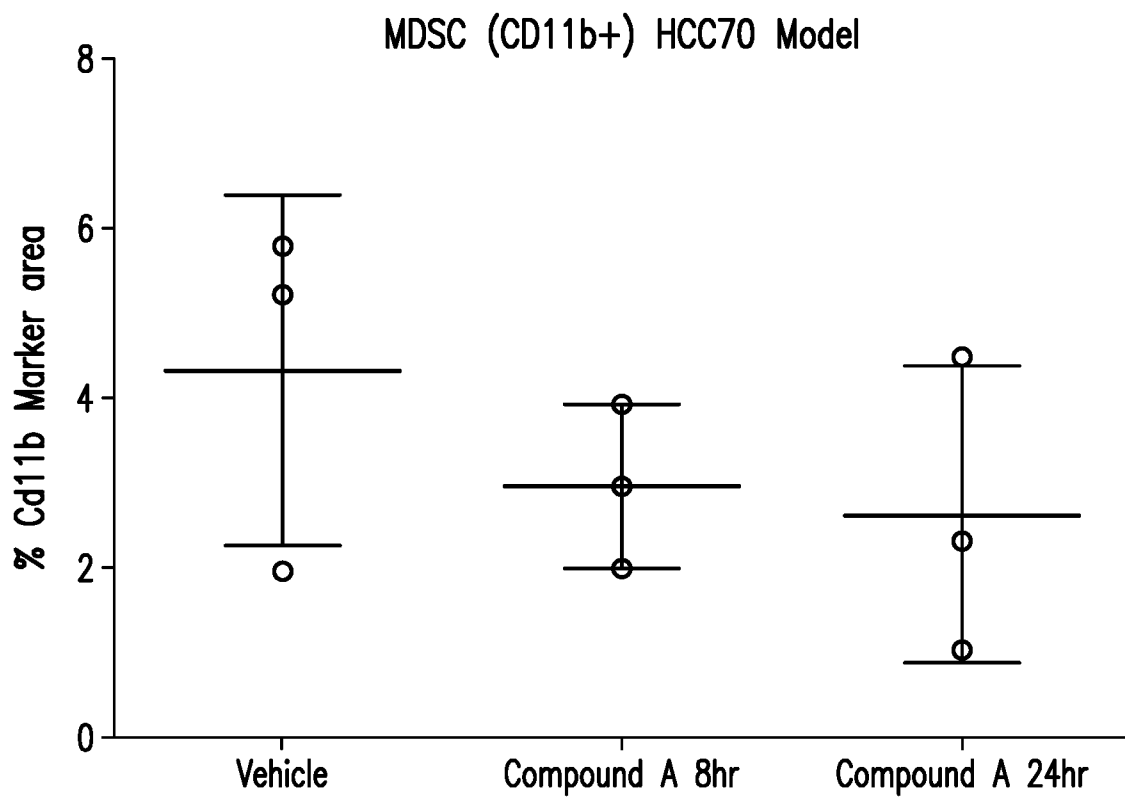


FIG. 13

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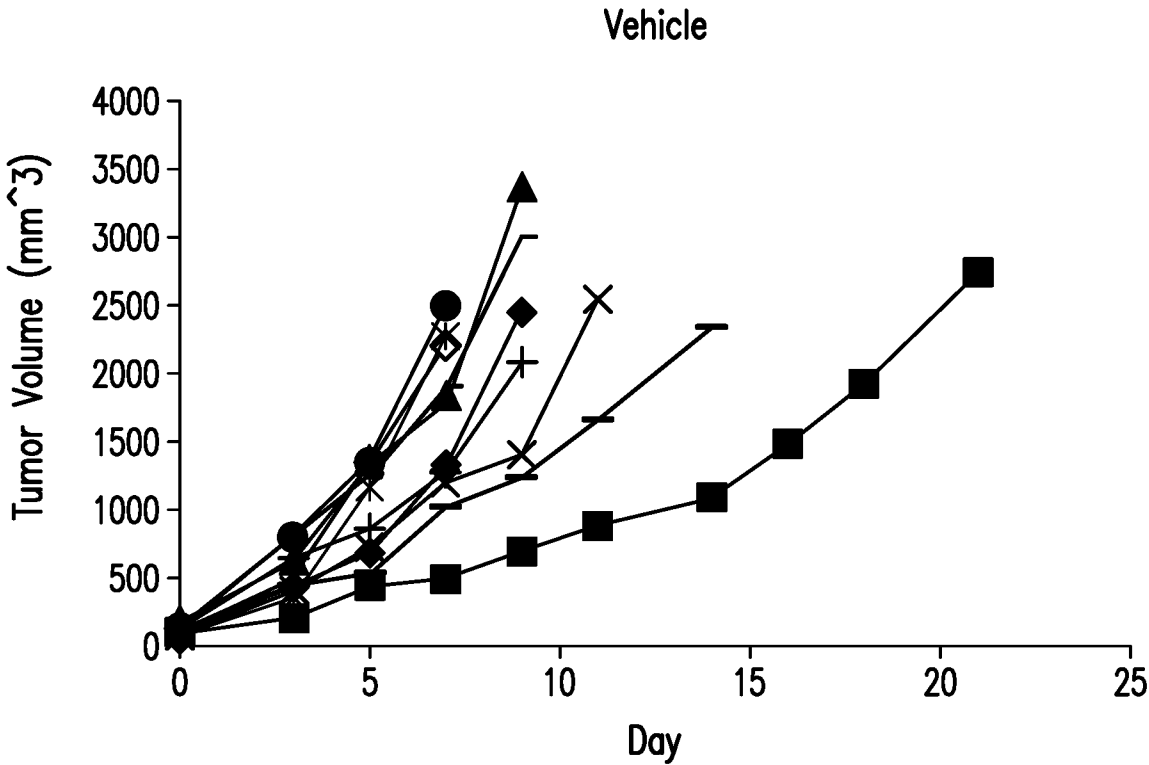


FIG. 14

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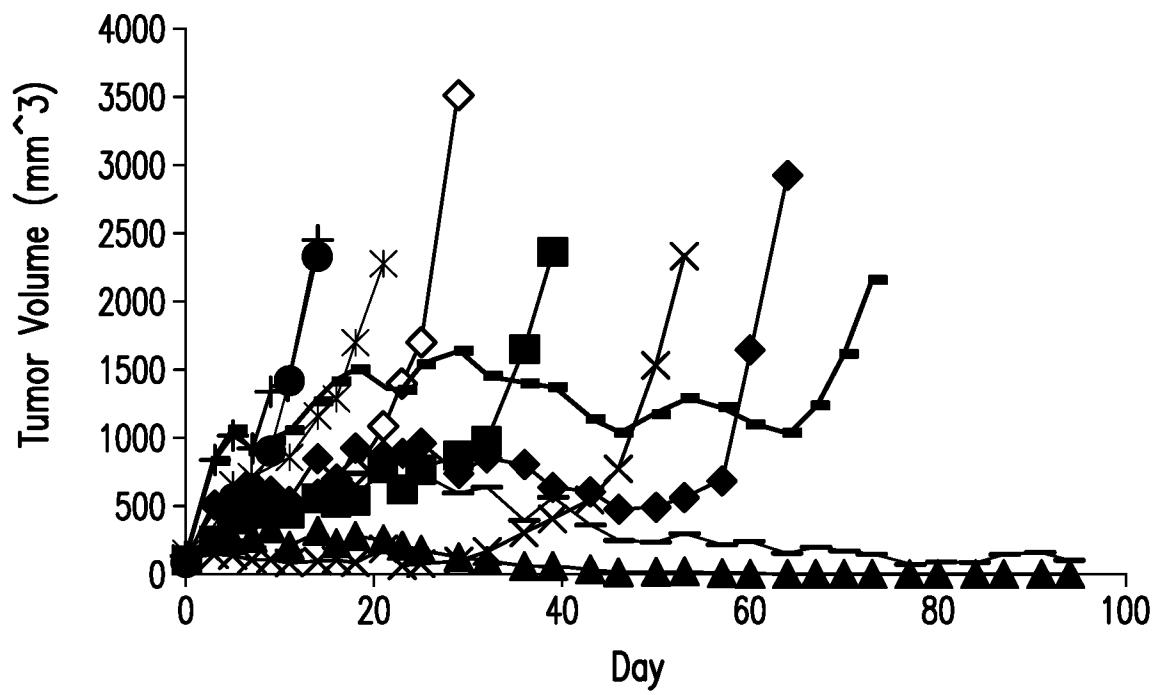


FIG. 15

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anti-PD-1 10mg/kg

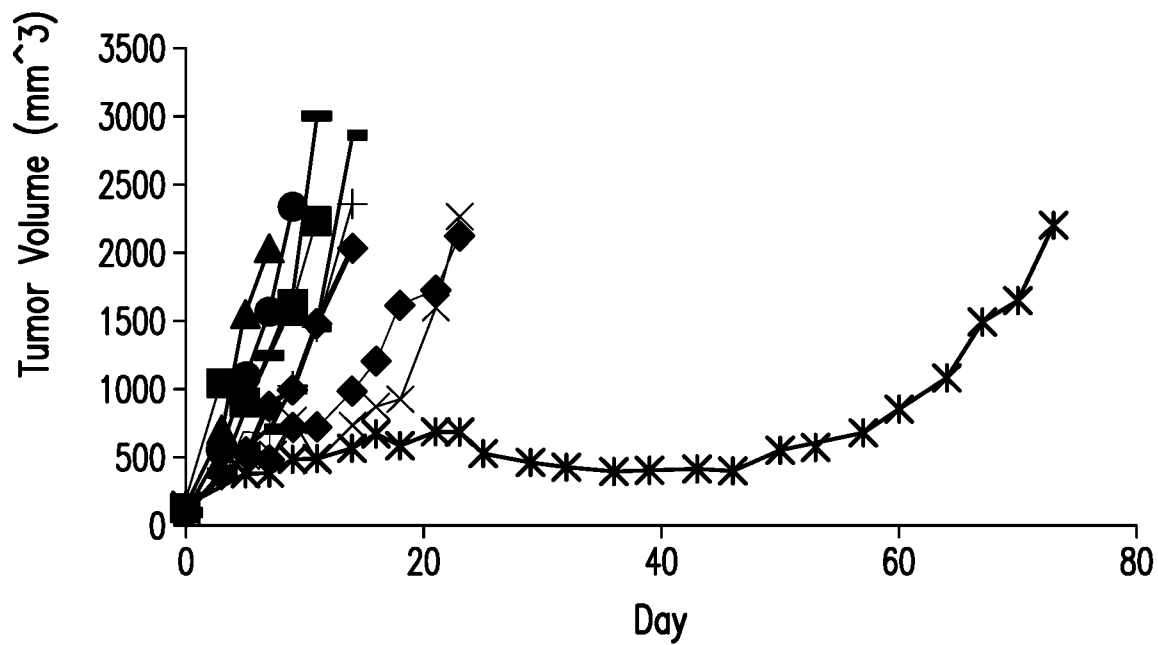


FIG. 16

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Compound A + anti-PD-1

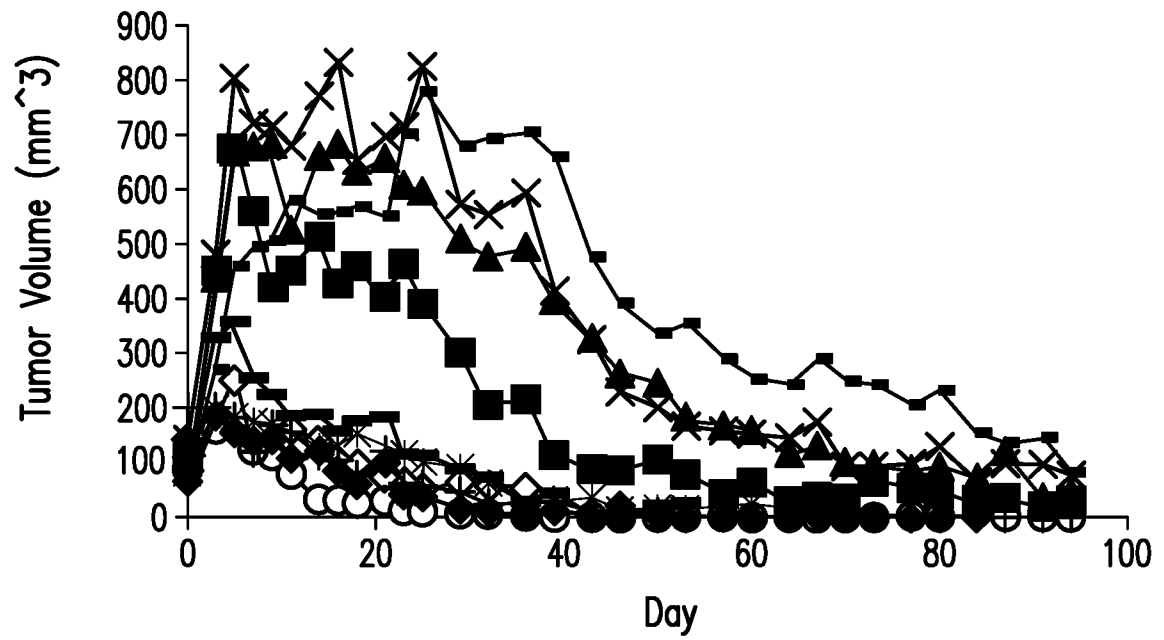


FIG. 17

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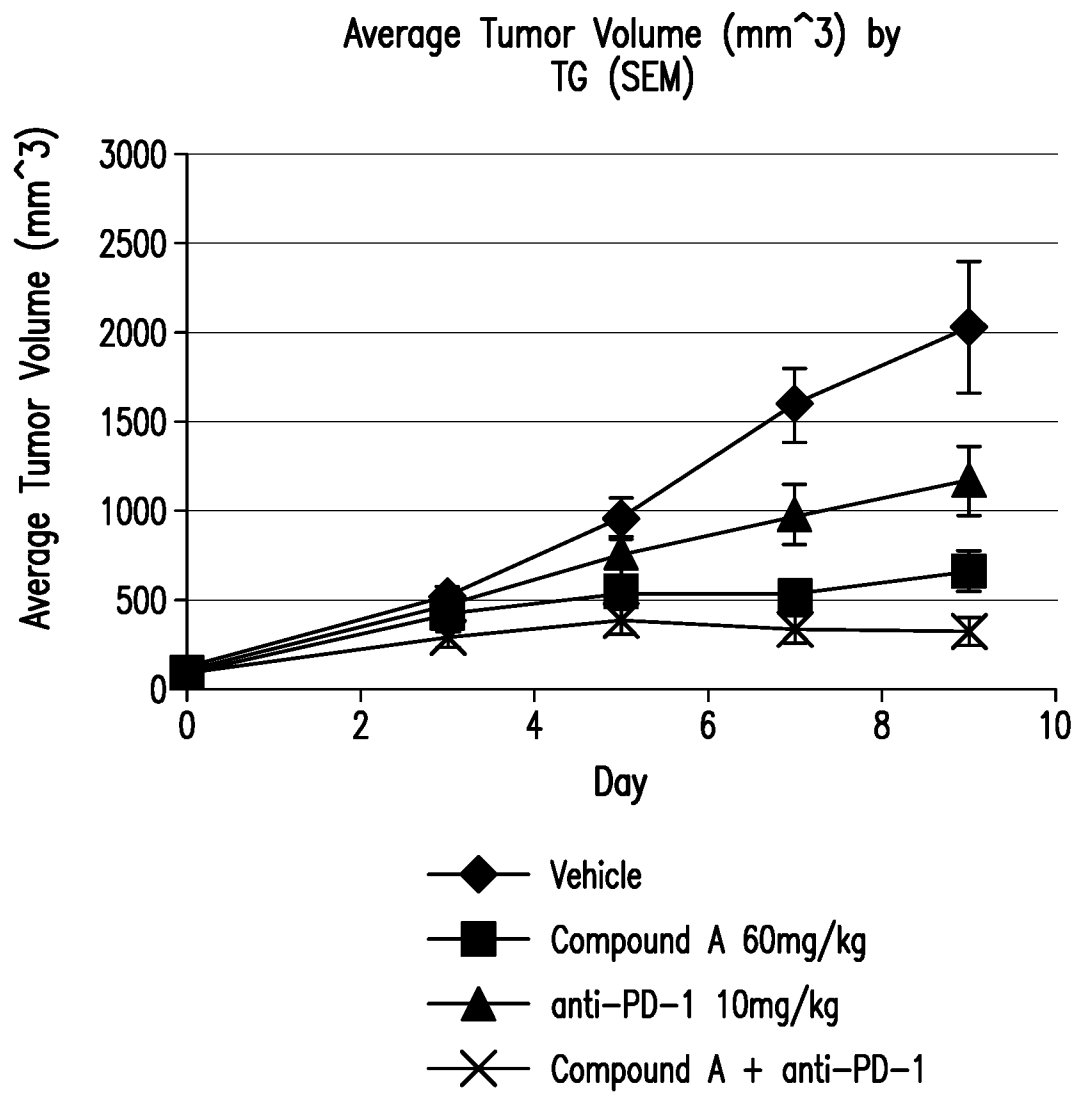
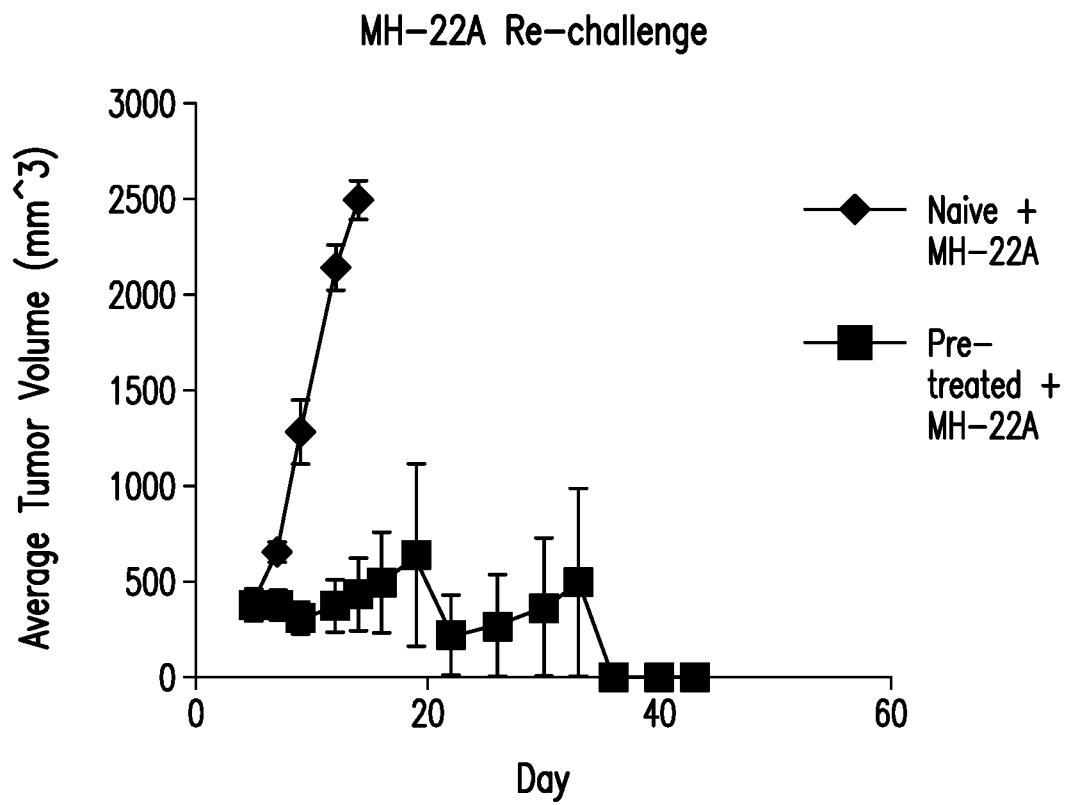


FIG. 18

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**FIG. 19**

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Pre-treated MH-22A

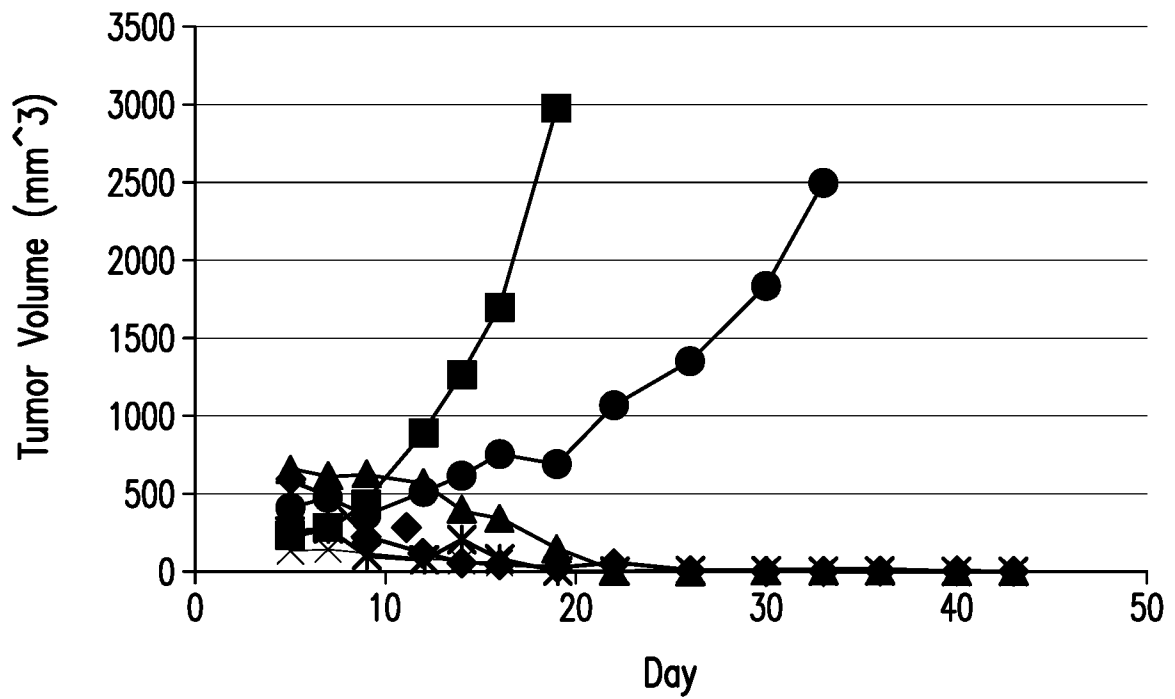


FIG. 20

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2017/034786

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/437 A61K39/395 A61K45/06 A61P35/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, CHEM ABS Data, WPI Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2011/152273 A1 (ARIKAWA YASUYOSHI [JP] ET AL) 23 June 2011 (2011-06-23)	1-3,9-36
Y	page 1, paragraph 2 page 5, paragraphs 157, 161 page 25, paragraph 301 page 25, paragraph 303 - paragraph 304 page 26, paragraph 309 page 26, paragraph 315 page 27, paragraph 321 claim 32 page 48; example 28	1-37
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☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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Date of the actual completion of the international search

25 July 2017

Date of mailing of the international search report

02/08/2017

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Authorized officer

Terenzi, Carla

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2017/034786

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	G. K. PHILIPS ET AL: "Therapeutic uses of anti-PD-1 and anti-PD-L1 antibodies", INTERNATIONAL IMMUNOLOGY, vol. 27, no. 1, 16 October 2014 (2014-10-16), pages 39-46, XP055217958, ISSN: 0953-8178, DOI: 10.1093/intimm/dxu095 abstract page 40, right-hand column, line 40 - page 41, left-hand column, line 7 page 41, line 9 - page 42, line 23	1-37
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Information on patent family members

International application No

PCT/US2017/034786

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